

**Fused Cyclic Succinimide Compounds and Analogs
Thereof, Modulators of Nuclear Hormone Receptor Function**

Cross-Reference to Related Application

5 This application claims priority from U.S. Provisional Application Serial No. 60/271,672, filed February 27, 2001, incorporated herein by reference in its entirety.

Field of the Invention

10 The present invention relates to fused cyclic compounds, to methods of using such compounds in the treatment of nuclear hormone receptor-associated conditions such as cancer, and to pharmaceutical compositions containing such compounds.

Background of the Invention

15 Nuclear hormone receptors (NHR's) constitute a large super-family of ligand-dependent and sequence-specific transcription factors. Members of this family influence transcription either directly, through specific binding to the promoter target genes (Evans, in *Science* **240**: 889-895 (1988)), or indirectly, via protein-protein interactions with other transcription factors (Jonat et al., *Cell* **62**: 1189-1204 (1990), Schuele et al., *Cell* **62**: 1217-1226 (1990), and Yang-Yen et al., *Cell* **62**: 1205-1215 (1990)). The nuclear hormone receptor super-family (also known in the art as the "steroid/thyroid hormone receptor super-family") includes receptors for a variety of hydrophobic ligands, including cortisol, aldosterone, estrogen, progesterone, testosterone, vitamine D3, thyroid hormone and retinoic acid (Evans, 1988, *supra*). In addition to these conventional nuclear hormone receptors, the super-family 20 contains a number of proteins that have no known ligands, termed orphan nuclear hormone receptors (Mangelsdorf et al., *Cell* **83**: 835-839 (1995), O'Malley et al., *Mol. Endocrinol.* **10**: 1293 (1996), Enmark et al., *Mol. Endocrinol.* **10**, 1293-1307 (1996) and Giguere, *Endocrin. Rev.* **20**, 689-725 (1999)). The conventional nuclear hormone receptors are generally transactivators in the presence of ligand, and can either be 25 active repressors or transcriptionally inert in the absence of ligand. Some of the orphan receptors behave as if they are transcriptionally inert in the absence of ligand.



Others, however, behave as either constitutive activators or repressors. These orphan nuclear hormone receptors are either under the control of ubiquitous ligands that have not been identified, or do not need to bind ligand to exert these activities.

5 In common with other transcription factors, the nuclear hormone receptors have a modular structure, being comprised of three distinct domains: an N-terminal domain of variable size containing a transcriptional activation function AF-1, a highly conserved DNA binding domain and a moderately conserved ligand-binding domain. The ligand-binding domain is not only responsible for binding the specific ligand but
10 also contains a transcriptional activation function called AF-2 and a dimerisation domain (Wurtz et al., *Nature Struct. Biol.* **3**, 87-94 (1996), Parker et al., *Nature Struct. Biol.* **3**, 113-115 (1996) and Kumar et al., *Steroids* **64**, 310-319 (1999)). Although the overall protein sequence of these receptors can vary significantly, all share both a common structural arrangement indicative of divergence from an ancestral archetype,
15 and substantial homology (especially, sequence identity) at the ligand-binding domain.

The steroid binding nuclear hormone receptors (SB-NHR's) comprise a sub-family of nuclear hormone receptors. These receptors are related in that they share a stronger sequence homology to one another, particularly in the ligand binding domain
20 (LBD), than to the other members of the NHR super-family (Evans, 1988, *supra*) and they all utilize steroid based ligands. Some examples of this sub-family of NHR's are the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the aldosterone receptor (ALDR) and the steroid and xenobiotic receptor (SXR) (Evans *et*
25 *al.*, WO 99/35246). Based on the strong sequence homology in the LBD, several orphan receptors may also be members of the SB-NHR sub-family.

Consistent with the high sequence homology found in the LBD for each of the SB-NHR's, the natural ligands for each is derived from a common steroid core. Examples of some of the steroid based ligands utilized by members of the SB-NHR's
30 include cortisol, aldosterone, estrogen, progesterone, testosterone and dihydrotestosterone. Specificity of a particular steroid based ligand for one SB-NHR versus another is obtained by differential substitution about the steroid core. High

affinity binding to a particular SB-NHR, coupled with high level specificity for that particular SB-NHR, can be achieved with only minor structural changes about the steroid core (e.g., Waller et al., *Toxicol. Appl. Pharmacol.* **137**, 219-227 (1996) and Mekenyan et al., *Environ. Sci. Technol.* **31**, 3702-3711 (1997), binding affinity for

5 progesterone towards the androgen receptor as compared to testosterone).

Numerous synthetically derived steroidal and non-steroidal agonists and antagonists have been described for the members of the SB-NHR family. Many of these agonist and antagonist ligands are used clinically in man to treat a variety of medical conditions. RU486 is an example of a synthetic agonist of the PR, which is

10 utilized as a birth control agent (Vegeto et al., *Cell* **69**: 703-713 (1992)), and

Flutamide is an example of an antagonist of the AR, which is utilized for the treatment of prostate cancer (Neri et al, *Endo.* **91**, 427-437 (1972)). Tamoxifen is an example of a tissues specific modulator of the ER function, that is used in the treatment of breast cancer (Smigel, *J. Natl. Cancer Inst.* **90**, 647-648 (1998)).

15 Tamoxifen can function as an antagonist of the ER in breast tissue while acting as an agonist of the ER in bone (Grese et al., *Proc. Natl. Acad. Sci. USA* **94**, 14105-14110 (1997)). Because of the tissue selective effects seen for Tamoxifen, this agent and agents like it are referred to as "partial-agonist" or partial-antagonist". In addition to synthetically derived non-endogenous ligands, non-endogenous ligands for NHR's

20 can be obtained from food sources (Regal et al., *Proc. Soc. Exp. Biol. Med.* **223**, 372-378 (2000) and Hempstock et al., *J. Med. Food* **2**, 267-269 (1999)). The flavanoid phytoestrogens are an example of an unnatural ligand for SB-NHR's that are readily obtained from a food source such as soy (Quella et al., *J. Clin. Oncol.* **18**, 1068-1074 (2000) and Banz et al., *J. Med. Food* **2**, 271-273 (1999)). The ability to modulate the

25 transcriptional activity of individual NHR by the addition of a small molecule ligand, makes them ideal targets for the development of pharmaceutical agents for a variety of disease states.

As mentioned above, non-natural ligands can be synthetically engineered to serve as modulators of the function of NHR's. In the case of SB-NHR's, engineering 30 of an unnatural ligand can include the identification of a core structure which mimics the natural steroid core system. This can be achieved by random screening against several SB-NHR's or through directed approaches using the available crystal

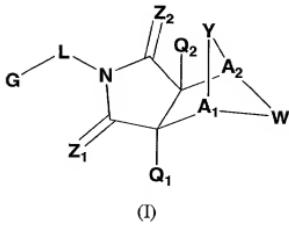
structures of a variety of NHR ligand binding domains (Bourguet et al., *Nature* **375**, 377-382 (1995), Brzozowski, et al., *Nature* **389**, 753-758 (1997), Shiu et al., *Cell* **95**, 927-937 (1998) and Tanenbaum et al., *Proc. Natl. Acad. Sci. USA* **95**, 5998-6003 (1998)). Differential substitution about such a steroid mimic core can provide agents

- 5 with selectivity for one receptor versus another. In addition, such modifications can be employed to obtain agents with agonist or antagonist activity for a particular SB-NHR. Differential substitution about the steroid mimic core can result in the formation of a series of high affinity agonists and antagonists with specificity for, for example, ER versus PR versus AR versus GR versus MR. Such an approach of
 10 differential substitution has been reported, for example, for quinoline based modulators of steroid NHR in *J. Med. Chem.*, 41, 623 (1999); WO 9749709; US 5696133; US 5696130; US 5696127; US 5693647; US 5693646; US 5688810; US 5688808 and WO 9619458, all incorporated herein by reference.

- 15 The compounds of the present invention comprise a core which serves as a steroid mimic, and are useful as modulators of the function of steroid binding nuclear hormone receptors, as well as other NHR as described following.

Summary of the Invention

- The present invention provides fused cyclic compounds of the following
 20 formula I and salts thereof, which compounds are especially useful as modulators of nuclear hormone receptor function:



- 25 As used in formula I, and throughout the specification, the symbols have the following meanings unless otherwise indicated, and are, for each occurrence, independently selected:

G is a cycloalkenyl, aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or

5 substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, $R^1OC=O$, $R^1C=O-O$, $R^1C=O$, $R^1C=S$, $R^1HNC=O$, $R^1R^2NC=O$, $HOCR^3R^3'$, nitro, R^1OCH_2 , R^1O , NH_2 , NR^4R^5 , SR^1 , $S=OR^1$, SO_2R^1 , SO_2OR^1 , $SO_2NR^1R^1'$, $(R^1O)(R^1'O)P=O$, oxo, $(R^1)(R^1')P=O$, or $(R^1')(NHR^1')P=O$;

Z_1 is O, S, NH, or NR⁶;

Z_2 is O, S, NH, or NR⁶; and

(i) Y is J-J'-J'' where J is $(CR^7R')_n$ and n = 0-3, J' is a bond, C=O, CR^7R'' ,

$\text{C}=\text{CR}^8\text{R}^{8'}, \text{R}^2\text{P}=\text{O}, \text{R}^2\text{P}=\text{S}, \text{R}^2\text{OP}=\text{O}, \text{R}^2\text{NHP}=\text{O}, \text{OP}=\text{OR}^2, \text{C}=\text{NR}^7,$

15 cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J'' is $(CR^7)^n$ and $n = 0-3$, where Y is not a bond;

W is CR⁷R^{7'}—CR⁷R^{7'}, CR⁸=CR^{8'}, CR⁷R^{7'}—C=O, cycloalkyl or substituted

cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or aryl or substituted aryl;

20 A₁ is CR⁷ or N; and

A_2 is CR⁷ or N; or alternatively

(ii) Y is absent;

W is CR⁷R^{7'}—CR⁷R^{7'}, CR⁸=CR^{8'}, CR⁷R^{7'}—C=O', cycloalkyl or substituted

cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted

25 heterocyclo, or aryl or substituted aryl;

A_1 is $CR^7R^{7'}$ or NR^7 ; and

A_2 is CB^7R^7 or NR^7 ; or alternatively

(iii) Y is absent; and

A_1, A_2 and W together are $-NR^7-N=N-$; and

30 Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl.

- heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC=O$, $R^4C=O$, $R^5R^6NC=O$, $HOCR^7R^7'$, nitro, R^1OCH_2 , R^1O , NH_2 , $C=OSR^1$, SO_2R^1 or NR^4R^5 ;
- 5 Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC=O$, $R^4C=O$, $R^5R^6NC=O$, $HOCR^7R^7'$, nitro, R^1OCH_2 , R^1O , NH_2 , $C=OSR^1$, SO_2R^1 or NR^4R^5 ;
- 10 L is a bond, $(CR^7R^7')n$, NH, NR^5 , $NH(CR^7R^7')n$, or $NR^5(CR^7R^7')n$, where $n = 0-3$;
- 10 R^1 and R^1' are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- 15 R^2 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- 20 R^3 and R^3' are each independently H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- 25 R^4 and R^4' are each independently H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;
- 30 R^5 is arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2 , thiol, alkylthio or substituted alkylthio;

5 R^4 is H, alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo,

10 cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or

15 substituted aryl, arylalkyl or substituted arylalkyl, $R^1C=O$, $R^1NHC=O$, SO_2OR^1 , or SO_2NR^1R' ;

20 R^5 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo,

25 cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C=O$, $R^1NHC=O$, SO_2R^1 , SO_2OR^1 , or SO_2NR^1R' ;

30 R^6 is alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo,

35 cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN , OH , OR^1 , $R^1C=O$, $R^1NHC=O$, SO_2R^1 , SO_2OR^1 , or SO_2NR^1R' ;

40 R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted

45 alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN , OR^1 , nitro, hydroxylamine,

50 hydroxylamide, amino, NHR^4 , NR^2R^5 , NOR^1 , thiol, alkylthio or substituted alkylthio, $R^1C=O$, $R^1OC=O$, $R^1C=O—O—$, $R^1NHC=O$, SO_2R^1 , SOR^1 , PO_3R^1R' , $R^1R'NC=O$, $C=OSR^1$, SO_2R^1 , SO_2OR^1 , or SO_2NR^1R' ; and

55 R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted

60 cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl,

heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR¹, amino, NHR⁴, NR²R⁵, NOR¹, alkylthio or substituted alkylthio, C=OSR¹, R¹OC=O, R¹C=O, R¹NHC=O, R¹R¹NC=O, SO₂OR¹, S=OR¹, SO₂R¹, PO₃R¹R¹, or SO₂NR¹R¹.

- 5 Compounds within formula I are novel; preferred such compounds are described further in the Examples herein.

The compounds of formula I and salts thereof comprise a core which can serve as a steroid mimic (and do not require the presence of a steroid-type (e.g., cyclopentanoperhydrophenanthrene analog) structure).

10

Further Description of the Invention

The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

The terms "alkyl" and "alk" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary such groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-

- 20 dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. "Substituted alkyl" refers to an alkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: halo (e.g., a single halo substituent or multiple halo substituents forming, in 25 the latter case, groups such as a perfluoroalkyl group or an alkyl group bearing Cl₃ or CF₃), alkoxy, alkylthio, hydroxy, carboxy (i.e., -COOH), alkoxy carbonyl, alkylcarbonyloxy, CN, amino (i.e., -NH₂), alkylamino, dialkylamino, carbamoyl or substituted carbamoyl, carbamate or substituted carbamate, urea or substituted urea, amidinyl or substituted amidinyl, thiol (i.e., -SH), aryl, heterocycle, cycloalkyl, 30 heterocycloalkyl, -S-aryl, -S-heterocycle, -S=O-aryl, -S=O-heterocycle, arylalkyl-O-, -S(O)₂-aryl, -S(O)₂-heterocycle, -NHS(O)₂-aryl, -NHS(O)₂-heterocycle,

- NHS(O)₂NH-aryl, -NHS(O)₂NH-heterocycle, -P(O)₂-aryl, -P(O)₂-heterocycle,
-NHP(O)₂-aryl, -NHP(O)₂-heterocycle, -NHP(O)₂NH-aryl, -NHP(O)₂NH-heterocycle,
-O-aryl, -O-heterocycle, -NH-aryl, -NH-heterocycle, -NHC=O-aryl, -NHC=O-alkyl,
-NHC=O-heterocycle, -OC=O-aryl, -OC=O-heterocycle, -NHC=ONH-aryl,
- 5 -NHC=ONH-heterocycle, -OC=OO-alkyl, -OC=OO-aryl, -OC=OO-heterocycle, -
OC=ONH-aryl, -OC=ONH-heterocycle, -NHC=OO-aryl, -NHC=OO-heterocycle, -
NHC=OO-alkyl, -C=ONH-aryl, -C=ONH-heterocycle, -C=OO-aryl,
-C=OO-heterocycle, -N(alkyl)S(O)₂-aryl, -N(alkyl)S(O)₂-heterocycle,
-N(alkyl)S(O)₂NH-aryl, -N(alkyl)S(O)₂NH-heterocycle, -N(alkyl)P(O)₂-aryl,
- 10 -N(alkyl)P(O)₂-heterocycle, -N(alkyl)P(O)₂NH-aryl, -N(alkyl)P(O)₂NH-heterocycle,
-N(alkyl)-aryl, -N(alkyl)-heterocycle, -N(alkyl)C=O-aryl, -N(alkyl)C=O-heterocycle,
N(alkyl)C=ONH-aryl, -N(alkyl)C=ONH-heterocycle, -OC=ON(alkyl)-aryl,
-OC=ON(alkyl)-heterocycle, -N(alkyl)C=OO-aryl, -N(alkyl)C=OO-heterocycle,
-C=ON(alkyl)-aryl, -C=ON(alkyl)-heterocycle, -NHS(O)₂N(alkyl)-aryl,
- 15 -NHS(O)₂N(alkyl)-heterocycle, -NHP(O)₂N(alkyl)-aryl,
NHP(O)₂N(alkyl)-heterocycle, -NHC=ON(alkyl)-aryl, -NHC=ON(alkyl)-heterocycle,
-N(alkyl)S(O)₂N(alkyl)-aryl, -N(alkyl)S(O)₂N(alkyl)-heterocycle,
-N(alkyl)P(O)₂N(alkyl)-aryl, -N(alkyl)P(O)₂N(alkyl)-heterocycle,
-N(alkyl)C=ON(alkyl)-aryl, and -N(alkyl)C=ON(alkyl)-heterocycle. In the
- 20 aforementioned exemplary substituents, in each instance, groups such as "alkyl",
"aryl" and "heterocycle" can themselves be optionally substituted; for example,
"alkyl" in the group "NCH=OO-alkyl" recited above can be optionally substituted so
that both "NHC=OO-alkyl" and "NHC=OO-substituted alkyl" are exemplary
substituents.
- 25 The term "alkenyl" refers to a straight or branched chain hydrocarbon radical
containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond.
Exemplary such groups include ethenyl or allyl. "Substituted alkenyl" refers to an
alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents,
at any available point of attachment. Exemplary substituents include, but are not
30 limited to, alkyl or substituted alkyl, as well as those groups recited above as
exemplary alkyl substituents.

The term "alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond.

Exemplary such groups include ethynyl. "Substituted alkynyl" refers to an alkynyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any

5 available point of attachment. Exemplary substituents include, but are not limited to, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents.

The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups

10 include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, nitro, cyano, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously

15 mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially cycloalkenyl or substituted cycloalkenyl.

The term "cycloalkenyl" refers to a partially unsaturated cyclic hydrocarbon group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups

20 include cyclobutenyl, cyclopentenyl, cyclohexenyl, etc. "Substituted cycloalkenyl" refers to a cycloalkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to nitro, cyano, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as

25 preferred aryl substituents in the definition for G. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially cycloalkyl or substituted cycloalkyl, or aryl or substituted aryl.

The terms "alkoxy" or "alkylthio" refer to an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively. The

30 terms "substituted alkoxy" or "substituted alkylthio" refer to a substituted alkyl group as described above bonded through an oxygen or sulfur linkage, respectively.

The term "alkoxycarbonyl" refers to an alkoxy group bonded through a carbonyl group.

The term "alkylcarbonyl" refers to an alkyl group bonded through a carbonyl group. The term "alkylcarbonyloxy" refers to an alkylcarbonyl group bonded through an oxygen linkage.

5 The terms "arylalkyl", "substituted arylalkyl," "cycloalkylalkyl," "substituted cycloalkylalkyl," "cycloalkenylalkyl", "substituted cycloalkenylalkyl", "heterocycloalkyl" and "substituted heterocycloalkyl" refer to aryl, cycloalkyl, cycloalkenyl and heterocyclo groups bonded through an alkyl group, substituted on 10 the aryl, cycloalkyl, cycloalkenyl or heterocyclo and/or the alkyl group where indicated as "substituted."

The term "aryl" refers to cyclic, aromatic hydrocarbon groups which have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two or more aromatic rings (bicyclic, etc.), the aromatic

15 rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl, phenanthrenyl and the like). "Substituted aryl" refers to an aryl group substituted by one or more substituents, preferably 1,2,3,4 or 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, nitro, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, cyano, 20 alkyl-S(O)_m⁻ (m=0, 1 or 2), alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include fused cyclic substituents, such as heterocyclo or cycloalkenyl, or substituted heterocyclo or cycloalkenyl, groups (e.g., thereby forming a fluoroenyl, tetrahydronaphthalenyl, or 25 dihydroindenyl group).

"Carbamoyl" refers to the group -CONH- which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, alkylcarbonyl, hydroxyl and substituted nitrogen). "Carbamate" refers to the group -O-CO-NH- which is bonded 30 on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as those listed above). "Urea" refers to the group -NH-CO-NH- which is bonded on one end to the remainder of the molecule and on the other to

hydrogen or an organic moiety (such as those listed above). “Amidinyl” refers to the group $-\text{C}(\text{=NH})(\text{NH}_2)$. “Substituted carbamoyl,” “substituted carbamate,” “substituted urea” and “substituted amidinyl” refer to carbamoyl, carbamate, urea or amidinyl groups as described above in which one more of the hydrogen groups are 5 replaced by an organic moiety (such as those listed above).

The terms “heterocycle”, “heterocyclic” and “heterocyclo” refer to fully saturated, or partially or fully unsaturated, including aromatic (i.e., “heteroaryl”) 10 cyclic groups (for example, 3 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term “heteroarylium” refers to a heteroaryl group bearing a quaternary nitrogen atom and 15 thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include ethylene oxide, azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiadiazolidinyl, 20 isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane 25 and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, 30 pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl) or furo[2,3-b]pyridinyl), dihydrobenzodioxinyl, dihydrodioxidobenzothiophenyl, dihydroisoindolyl, dihydroindolyl, dihydroquinolinyl, dihydroquinazolinyl (such as

3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

- “Substituted heterocycle,” “substituted heterocyclic,” and “substituted heterocyclo” (such as “substituted heteroaryl”) refer to heterocycle, heterocyclic or heterocyclo groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, nitro, oxo (i.e., = O), cyano, alkyl-S(O)_m⁻ (m = 0, 1 or 2), alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as preferred heterocyclo substituents in the definition for G.

The term “quaternary nitrogen” refers to a tetravalent positively charged nitrogen atom including, for example, the positively charged nitrogen in a

- 15 tetraalkylammonium group (e.g., tetramethylammonium, N-methylpyridinium), the positively charged nitrogen in protonated ammonium species (e.g., trimethylhydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g., N-methyl-morpholine-N-oxide, pyridine-N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g., N-aminopyridinium).

- 20 The terms “halogen” or “halo” refer to chlorine, bromine, fluorine or iodine.

The terms “hydroxylamine” and “hydroxylamide” refer to the groups OH-NH- and OH-NH-CO-, respectively.

When a functional group is termed “protected”, this means that the group is in modified form to mitigate, especially preclude, undesired side reactions at the

- 25 protected site. Suitable protecting groups for the methods and compounds described herein include, without limitation, those described in standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

When a term such as “(CRR)_n” is used, it denotes an optionally substituted alkyl chain existing between the two fragments to which it is bonded, the length of

- 30 which chain is defined by the range described for the term n. An example of this is n=0-3, implying from zero to three (CRR) units existing between the two fragments, which are attached to the primary and terminal (CRR) units. In the situation where

the term n is set to zero (n = 0) then a bond exists between the two fragments attached to (CRR).

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

5 Divalent groups, such as those in the definition of W (e.g., CR⁷R⁷-C=O), may be bonded in either direction to the remainder of the molecule (e.g.,
$$\begin{matrix} -A_1-CR^7R^7-C=O-A_2^- \text{ or, } -A_1-C=O-CR^7R^7-A_2^- \end{matrix}$$
 for the aforementioned group within the definition of W).

Carboxylate anion refers to a negatively charged group -COO⁻.

10 The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety,
15 such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolation or purification steps which may be employed during
20 preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety, such as but not
25 limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates,
30 cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates,

hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (e.g., 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates,

naphthalenesulfonates (e.g., 2-naphthalenesulfonates), nicotinates, nitrates, oxalates, pectinates, persulfates, phenylpropionates (e.g., 3-phenylpropionates), phosphates,

- 5 picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of formula I which contain an acidic moiety, such but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic

- 10 bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-

bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-

- 15 glycamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides),
20 aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I include, for example, hydrates.

Compounds of the formula I, and salts thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

- 30 All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be

substantially free of other isomers (e.g., as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the IUPAC 1974 Recommendations.

- 5 The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

10 All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both cis (*Z*) and trans (*E*) alkene isomers, as well as cis and trans isomers of cyclic hydrocarbon or heterocyclo

- 15 rings. In certain cases, for example, the exo or endo conformation can be preferred for the fused ring system bonded to G-L in formula I. As can be appreciated, the preferred configuration can be a function of the particular compound and its preferred activity. Separation of configurational isomers can be achieved by any suitable method, such as column chromatography.

- 20 Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

Embodiments indicated herein as exemplary or preferred are intended to be illustrative and not limiting.

25

Methods of Preparation

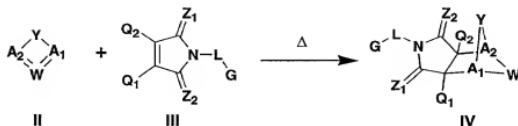
The compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes I to IV. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Combinatorial techniques may be employed in the preparation of compounds, for example, where the intermediates possess groups

- suitable for these techniques. See the following which describe other methods which may be employed in the preparation of compounds of the present invention: Li, *et al.*, *Eur. J. Org. Chem.* **9**, 1841-1850 (1998); Li, Y-Q, *Synlett.* **5**, 461-464 (1996); Thiemann, *et al.*, *Bull. Chem. Soc. Jpn.* **67**, 1886-1893 (1994); Tsuge *et al.*, *Heterocycles* **14**, 423-428 (1980); Ward *et al.*, *Can J. Chem.* **75**, 681-693 (1997); Ward *et al.*, *Can J. Chem.* **69**, 1487-1497 (1991); Ward *et al.*, *Tetrahedron Lett.* **31**, 845-848 (1990); Fleming *et al.*, *J. Org. Chem.* **44**, 2280-2282 (1979); Jankowski *et al.*, *J. Organomet. Chem.* **595**, 109-113 (2000); Keglevich *et al.*, *J. Organomet. Chem.* **579**, 182-189 (1999); Keglevich *et al.*, *J. Organomet. Chem.* **570**, 49-539 (1998); Jankowski *et al.*, *Hetroat. Chem.* **7**, 369-374 (1996); Jankowski *et al.*, *J. Am. Chem. Soc.* **113**, 7011-7017 (1991); Quin *et al.*, *Tetrahedron Lett.* **31**, 6473-6476 (1990); Quin *et al.*, *J. Org. Chem.* **59**, 120-129 (1994); Quin *et al.*, *J. Org. Chem.* **58**, 6212-6216 (1993); Quin *et al.*, *Phosphorous, Sulfur Silicon Relat. Elem.* **63**, 349-362 (1991); Quin *et al.*, *Hetroat. Chem.* **2**, 359-367 (1991); Hussong *et al.*, *Phosphorus Sulfur.* **25**, 201-212 (1985); Quin *et al.*, *J. Org. Chem.* **51**, 3341-3347 (1986); Myers *et al.*, *J. Am. Chem. Soc.* **114**, 5684-5692 (1992); Myers *et al.*, *J. Am. Chem. Soc.* **113**, 6682-6683 (1991); Shen *et al.*, US Patent No. 5817679; Cordone *et al.*, *J. Am. Chem. Soc.* **111**, 5969-5970 (1989); Jung *et al.*, *J. Chem. Soc. Commun.* 630-632 (1984); Lay *et al.*, *J. Am. Chem. Soc.* **104**, 7658-7659 (1982); Gonzalez *et al.*, *J. Am. Chem. Soc.* **117**, 3405-3421 (1995); Kreher *et al.*, *Chem Ber.* **125**, 183-189 (1992); Simig *et al.*, *Synlett.* **7**, 425-426 (1990); Sha *et al.*, *J. Org. Chem.* **55**, 2446-2450 (1990); Drew *et al.*, *J. Chem. Soc., Perkin Trans. I* **7**, 1277-1284 (1985); Kreher *et al.*, *Anorg. Chem., Org. Chem.* **31B**, 599-604 (1976); Avalos *et al.*, *Tetrahedron Lett.* **39**, 9301-9304 (1998); Gousse *et al.*, *Macromolecules* **31**, 314-321 (1998); Mikhailyuchenko *et al.*, *Khim. Geterotsikl. Soedin.* **6**, 751-758 (1993); Lubowitz *et al.*, US Patent No. 4476184; Padwa *et al.*, *J. Org. Chem.* **61**, 3706-3714 (1996); Schlessinger *et al.*, *J. Org. Chem.* **59**, 3246-3247 (1994); Buchmeiser *et al.*, WO Publication No. 9827423; Tanabe *et al.*, Japanese Patent Document JP 07144477; Mochizuki *et al.*, Japanese Patent Document JP 63170383; Hosoda *et al.*, Japanese Patent Document JP 62053963; Onaka *et al.*, Japanese Patent Document JP 62053964; Kato *et al.*, Japanese Patent Document JP 53086035; Kato *et al.*, Japanese Patent Document JP

51088631; Tottori *et al.*, Japanese Patent Document JP 49124225; Augustin *et al.*, German Patent Document DD101271; Title *et al.*, French Patent Document FR 2031538; Gousse *et al.*, *Polym. Int.* **48**, 723-731 (1999); Padwa *et al.*, *J. Org. Chem.* **62**, 4088-4096 (1997); Theurillat-Moritz *et al.*, *Tetrahedron: Asymmetry* **7**, 3163-5 3168 (1996); Mathews *et al.*, *J. Carbohydr. Chem.* **14**, 287-97 (1995); Srivastava *et al.*, *Natl. Acad. Sci. Lett. (India)* **15**, 41-44 (1992); Mayorga *et al.*, *Rev. Cubana Quim.* **4**, 1-6 (1988); Kondoli *et al.*, *J. Chem. Res., Synop.* **3**, 76 (1987); Primelles *et al.*, *Cent. Azucar* **7**-14 (1985); Solov'eva *et al.*, *Khim. Geterotsikl. Soedin.* **5**, 613-15 (1984); Liu *et al.*, *Yaoxue Xuebao* **18**, 752-759 (1983); Joshi *et al.*, *Indian J. Chem., Sect. B* **22B**, 131-135 (1983); Amos *et al.*, WO Publication No. 9829495; Odagiri *et al.*, US Patent No. 4670536; Gallucci *et al.*, European Patent Document EP 355435; Redmore, D. US Patent No. 3821232; Nakano *et al.*, *Heterocycles* **35**, 37-40 (1993); Tomisawa *et al.*, *Chem. Pharm. Bull.* **36**, 1692-1697 (1988); Krow *et al.*, *J. Heterocycl. Chem.* **22**, 131-135 (1985); Krow *et al.*, *J. Org. Chem.* **47**, 1989-1993 10 (1982); Liu *et al.*, *Yaoxue Xuebao* **18**, 752-759 (1983); Nishikawa *et al.*, *Yaoxue Xuebao* JP 01061457; and/or Rice *et al.*, *J. Med. Chem.* **11**, 183-185 (1968).

All documents cited in the present specification, such as those cited in this "Methods of Preparation" as well as other sections herein, are incorporated herein by reference in their entirety. Reference to any document herein is not to be construed as an admission that such document is prior art.

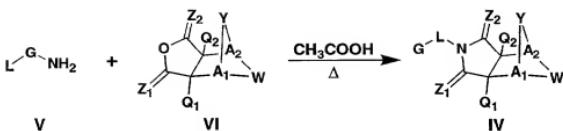
Scheme I



As illustrated in Scheme I, a diene of formula II can be reacted with a dienophile of formula III, under conditions readily selected by one skilled in the art (such as by the addition of heat ("Δ")), to obtain a compound of formula IV, which is a compound of formula I. An intermediate diene of formula II can be obtained from commercial sources or readily made by one skilled in the art, for example, in accordance with the following literature documents and the references found therein:

Hofman *et al.*, *J. Agric. Food Chem.* **45**, 898-906 (1997); Baciocchi *et al.*, *J. Chem. Soc., Perkin Trans. 2* **8**, 821-824 (1975); Wu *et al.*, *J. Heterocycles* **38**, 1507-1518 (1994); Yin *et al.*, *Tetrahedron Lett.* **38**, 5953-5954 (1997); Mic'ovic' *et al.*, *Tetrahedron* **20**, 2279-2287 (1964); Gorbunova *et al.*, *J. Org. Chem.* **35**, 1557-1566 (1999); Rassu *et al.*, *Chem. Soc. Rev.* **29**, 109-118 (2000); Kaberdin *et al.*, *Russ. Chem. Rev.* **68**, 765-779 (1999); Barluenga *et al.*, *Aldrichimica Acta* **32**, 4-15 (1999); Bogdanowicz-Szwed *et al.*, *Pol. Wiad. Chem.* **52**, 821-842 (1998); Casiraghi *et al.*, *Adv. Asymmetric Synth.* **3**, 113-189 (1998); and/or Baeckvall *et al.*, *Chem. Rev.* **98**, 2291-2312 (1998). An intermediate dieneophile of formula III can be obtained from commercial sources or readily made by one skilled in the art, for example, in accordance with the following literature references and the references found therein: Deshpande *et al.*, *Heterocycles* **51**, 2159-2162 (1999); Seijas *et al.*, *J. Chem. Res., Synop.* **7**, 420-421 (1999); Langer *et al.*, *Eur. J. Org. Chem.* **7**, 1467-1470 (1998); Kita *et al.*, Japanese Patent Document JP 09194458; Lopez-Alvarado *et al.*, *J. Org. Chem.* **61**, 5865-5870 (1996); Condon *et al.*, US Patent No. 5523277; Sasakihara *et al.*, Japanese Patent Document JP 04290868; Igarashi *et al.*, Japanese Patent Document JP 04149173; Aoyama *et al.*, Japanese Patent Document JP 04134063; Aoyama *et al.*, Japanese Patent Document JP 04134062; Pastor *et al.*, *J. Org. Chem.* **53**, 5776-5779 (1988); and/or Takahashi *et al.*, *Chem. Lett.* **6**, 1229-1232 (1987).

Scheme II



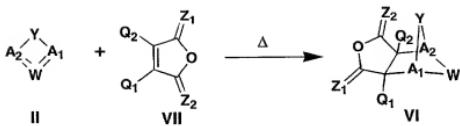
- 5 As illustrated in Scheme II, compounds of formula I can be obtained by reaction of a primary amine of formula V with a substituted anhydride-like intermediate of formula VI, for example, in a solvent such as acetic acid with or without heating, to yield a compound of formula IV, which is a compound of formula I. Primary amines of formula V can be obtained from commercial sources or readily
- 10 synthesized by one skilled in the art. Anhydride-like agents of formula VI can be obtained from commercial sources or readily synthesized by one skilled in the art. The documents listed following describe exemplary approaches for the synthesis of intermediates of formula VI as well as synthetic approaches which can be applied to the synthesis of compounds of formula IV (all incorporated herein by reference in
- 15 their entirety): Kohler, E. P.; Tishler, M.; Potter, H.; Thompson, H. T. *J. Am. Chem. Soc.* 1939, 1057-1061; Yur'ev, Y. K.; Zefirov, N. S. *J. Gen. Chem. U.S.S.R. (Engl. Transl.)* 1961, 31, 772-5; Norman G. Gaylord US Patent No. 3,995,099; Schueler, P. E.; Rhodes, Y. E. *J. Org. Chem.* 1974, 39, 2063-9; Ishitobi, H.; Tanida, H; Tsuji, T. *Bull. Chem. Soc. Japan* 1971, 44, 2993-3000; Stájer, G.; Virág, M.; Szabó, A. E.;
- 20 Bernáth, G.; Sohár, P.; Sillanpää, R. *Acta. Chem. Scand.* 1996, 50, 922-30; Hart, H.; Ghosh, T. *Tetrahedron Lett.* 1988, 29, 881-884; Kato, M.; Yamamoto, S.; Yoshihara, T.; Furuichi, K.; Miwa, T. *Chem. Lett.* 1987, 1823-1826; Kottwitz, J.; Vorbrüggen, H. *Synthesis* 1995, 636-637; Creary, X. *J. Org. Chem.* 1975, 40, 3326-3331; Alder, K.; Ache, H.-J.; Flock, F. H. *Chem. Ber.* 1960, 93, 1888-1895; Toder, B. H.; Branca, S. J.; Dieter, R. K.; Smith, A. B. III *Synth. Commun.* 1975, 5, 435-439; Sprague, P. W.; Heikes, J. E.; Gougotas, J. Z.; Malley, M. F.; Harris, D. N.; and/or Greenberg, R. J. *Med. Chem.* 1985, 28, 1580-1590.

The aforementioned approach(es) can be applied in a combinatorial fashion, for example, by utilizing a multi-well reaction block such as is described in Waldemar Ruediger, Wen-Jeng Li, John W., Allen Jr., and Harold N. Weller III, US Patent No. 5,961,925, Apparatus for Synthesis of Multiple Organic Compounds With Pinch

- 5 Valve Block (incorporated herein by reference in its entirety). By utilizing the above-mentioned multi-well reaction block, one can, for example, perform multiples of 96 reactions at a time. Solvent can then be removed from the reaction tubes without removal from the reaction block and the crude products can be precipitated using a base such as sodium bicarbonate. The precipitates can be collected by filtration of the
- 10 reaction block and then the desired products can be transferred directly to 96 well plates for screening. In this fashion, a large array of compounds of formula I can be synthesized, and tests conducted as desired by an automated approach.

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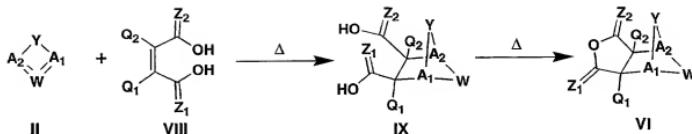
Scheme III



5 Scheme III describes a method for preparing an intermediate compound of formula VI which can be used to synthesize a compound of formula I, as described in Scheme II. As described in Scheme III, a diene of formula II can be reacted with a dieneophile of formula VII to yield the intermediate of formula VI. The methods applied to obtain such a transformation are analogous to those described in Scheme I.

10

Scheme IV



Scheme IV describes a method for preparing an intermediate compound of formula VI which can be used to synthesize a compound of formula I, as described in Scheme II. As shown in Scheme IV, a diene of formula II can be reacted with a dieneophile of formula VIII to yield the intermediate of formula IX. The intermediate of formula IX can be dehydrated to an anhydride-like intermediate of formula VI. Dehydration of the bis-acid intermediate of formula IX to can be achieved by a variety of methods, such as those known to one skilled in the art and described in the following documents and the references embodied therein: Sprague *et al.*, *J. Med. Chem.* **28**, 1580-1590 (1985); and/or Retemi *et al.*, *J. Org. Chem.* **61**, 6296-6301 (1996).

15 Preferred Compounds

A preferred subgenus of the compounds of the present invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the following substituents are as defined below:

G is a cycloalkenyl, an aryl (preferably phenyl or naphthyl), or heterocyclo (e.g.,

20 heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, $R^1OC=O$, $R^1C=O-O-$, $R^1C=O$, $R^1C=S$, $R^1HNC=O$, $R^1R^2NC=O$, $HOCR^3R^3'$, nitro, R^1OCH_2 , R^1O , NH_2 , NR^4R^5 , SR^1 , $S=OR^1$,

SO_2R^1 , SO_2OR^1 , $\text{SO}_2\text{NR}^1\text{R}^1'$, $(\text{R}^1\text{O})(\text{R}^1'\text{O})\text{P=O}$, oxo, $(\text{R}^1)(\text{R}^1')\text{P=O}$, or
 $(\text{R}^1')(\text{NHR}^1)\text{P=O}$;

Z_1 is O or S;

Z_2 is O or S; and

- 5 (i) Y is $-(\text{CR}^7\text{R}^7)_n$ and $n=1-3$, $\text{C}=\text{CR}^8\text{R}^8'$, $\text{C}=\text{O}$, cycloalkyl or substituted cycloalkyl,
cycloalkenyl or substituted cycloalkenyl, or aryl or substituted aryl;
W is $\text{CR}^7\text{R}^7'—\text{CR}^7\text{R}^7'$, $\text{CR}^8=\text{CR}^8'$, $\text{CR}^7\text{R}^7'—\text{C}=\text{O}$, cycloalkyl or substituted
cycloalkyl, or aryl or substituted aryl;

A_1 is CR^7 ; and

- 10 A_2 is CR^7 ; or alternatively,

(ii) Y is absent;

W is $\text{CR}^7\text{R}^7'—\text{CR}^7\text{R}^7'$ or $\text{CR}^8=\text{CR}^8'$;

A_1 is CR^7 ; and

A_2 is CR^7 ; or alternatively,

- 15 (iii) Y is absent; and

A_1 , A_2 and W together are $-\text{NR}^7-\text{N}=\text{N}-$; and

Q_1 is H, alkyl or substituted alkyl;

Q_2 is H, alkyl or substituted alky; and

L is a bond, NH or NR^5 .

20

Use and Utility

- The compounds of the present invention modulate the function of nuclear hormone receptors (NHR), and include compounds which are, for example, agonists, partial agonists, antagonists or partial antagonists of the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the steroid and xenobiotic receptor (SXR), other steroid binding NHR's, the Orphan receptors or other NHR's. Selective modulation of one such NHR relative to others within the NHR family is preferred.
"Modulation" includes, for example, activation (e.g., agonist activity) or inhibition
(e.g., antagonist activity).

The present compounds are thus useful in the treatment of NHR-associated conditions. A "NHR-associated condition", as used herein, denotes a condition or disorder which can be treated by modulating the function of a NHR in a subject, wherein treatment comprises prevention, partial alleviation or cure of the condition or disorder. Modulation may occur locally, for example, within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition disorder.

The compounds of the present invention are useful for the treatment of a variety of conditions and disorders including, but not limited to, those described 10 following:

Compounds of formula I can be applied as agonists, partial agonists, antagonists, or partial antagonists of the estrogen receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the estrogen receptor pathway. Applications of said compounds include but are not limited to: osteoporosis, hot flushes, vaginal dryness, prostate cancer, breast cancer, 15 endometrial cancer, cancers expressing the estrogen receptor such as the aforementioned cancers and others, contraception, pregnancy termination, menopause, amenorrhea, and dysmenorrhea.

Compounds of formula I can be applied as agonists, partial agonists, 20 antagonists or partial antagonists of the progesterone receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the progesterone receptor pathway. Applications of said compounds include but are not limited to: breast cancer, other cancers containing the progesterone receptor, endometriosis, cachexia, contraception, menopause, cyclesynchrony, menignoma, 25 dysmenorrhea, fibroids, pregnancy termination, labor induction and osteoporosis.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the glucocorticoid receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the glucocorticoid receptor pathway. Applications of said compounds include but are not 30 limited to: inflammatory diseases, autoimmune diseases, prostate cancer, breast cancer, Alzheimer's disease, psychotic disorders, drug dependence, non-insulin dependent Diabetes Mellitus, and as dopamine receptor blocking agents or otherwise

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as agents for the treatment of dopamine receptor mediated disorders. Glucocorticoid receptor AP-1 ("GR AP-1") inhibitors (which compounds can, for example, avoid side effects connected with GR agonists) can be used as anti-inflammatory and immunosuppressive agents, for example, to treat a wide variety of inflammatory and autoimmune diseases. These diseases include without limitation: rheumatoid arthritis, 5 osteoarthritis, inflammatory bowel disease, asthma, chronic obstructive pulmonary disease, prevention of transplant rejection, multiple sclerosis, and psoriasis, among others. GR AP-1 inhibitors of the present invention can be employed together with known GR AP-1 inhibitors, such as the steroid prednisone (which is used to treat the 10 above diseases).

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the mineralocorticoid receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the mineralocorticoid receptor pathway. Applications of said 15 compounds include but are not limited to: drug withdrawal syndrome and inflammatory diseases.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the aldosterone receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the 20 aldosterone receptor pathway. One application of said compounds includes but is not limited to: congestive heart failure.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the androgen receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the 25 androgen receptor pathway. Applications of said compounds include but are not limited to: hirsutism, acne, seborrhea, Alzheimer's disease, androgenic alopecia, hypogonadism, hyperpilosity, benign prostate hypertrophy, adenomas and neoplasies of the prostate (such as advanced metastatic prostate cancer), treatment of benign or malignant tumor cells containing the androgen receptor such as is the case for breast, 30 brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers, pancreatic cancers, modulation of VCAM expression and applications therein for the treatment of heart disease, inflammation and immune modulations, modulation of VEGF expression and

the applications therein for use as antiangiogenic agents, osteoporosis, suppressing spermatogenesis, libido, cachexia, endometriosis, polycystic ovary syndrome, anorexia, androgen supplement for age related decreased testosterone levels in men, male menopause, male hormone replacement, male and female sexual dysfunction, 5 and inhibition of muscular atrophy in ambulatory patients. For example, pan AR modulation is contemplated, with prostate selective AR modulation ("SARM") being particularly preferred, such as for the treatment of early stage prostate cancers.

Compounds of formula I can be applied as (preferably, selective) antagonists of the mutated androgen receptor, for example, found in many tumor 10 lines. Examples of such mutants are those found in representative prostate tumor cell lines such as LNCap, (T877A mutation, Biophys. Acta, 187, 1052 (1990)), PCa2b, (L701H & T877A mutations, J. Urol., 162, 2192 (1999)) and CWR22, (H874Y mutation, Mol. Endo., 11, 450 (1997)). Applications of said compounds include but are not limited to: adenomas and neoplasies of the prostate, breast cancer and 15 endometrial cancer.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the steroid and xenobiotic receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the steroid and xenobiotic receptor pathway. Applications of said 20 compounds include but are not limited to: treatment of disregulation of cholesterol homeostasis, attenuation of metabolism of pharmaceutical agents by co-administration of an agent (compound of the present invention) which modulates the P450 regulator effects of SXR.

Along with the aforementioned NHR, there also exist a number of NHR for 25 which the activating or deactivating ligands may not be characterized. These proteins are classified as NHR due to strong sequence homology to other NHR, and are known as the Orphan receptors. Because the Orphan receptors demonstrate strong sequence homology to other NHR, compounds of formula I include those which serve as modulators of the function of the Orphan NHR. Orphan receptors which are 30 modulated by NHR modulators such as compounds within the scope of formula I are exemplified, but not limited to, those listed in Table 1. Exemplary therapeutic

applications of modulators of said Orphan receptors are also listed in Table 1, but are not limited to the examples therein.

5 **Table 1.** Exemplary Orphan nuclear hormone receptors, form (M = monomeric, D = heterodimeric, H = homodimeric), tissue expression and target therapeutic applications. (CNS=central nervous system)

<u>Receptor</u>	<u>Form</u>	<u>Tissue Expression</u>	<u>Target Therapeutic Application</u>
NURR1	M/D	Dopaminergic Neurons	Parkinson's Disease
RZR β	M	Brain (Pituitary), Muscle	Sleep Disorders
10 ROR α	M	Cerebellum, Purkinje Cells	Arthritis, Cerebellar Ataxia
NOR-1	M	Brain, Muscle, Heart, Adrenal, Thymus	CNS Disorders, Cancer
NGFI-B β	M/D	Brain	CNS Disorders
COUP-Tf α	H	Brain	CNS Disorders
15 COUP-TF β	H	Brain	CNS Disorders
COUP-TF γ	H	Brain	CNS Disorders
Nur77	H	Brain, Thymus, Adrenals	CNS Disorders
Rev-ErbA α	H	Muscle, Brain (Ubiquitous)	Obesity
HNF4 α	H	Liver, Kidney, Intestine	Diabetes
20 SF-1	M	Gonads, Pituitary	Metabolic Disorders
LXR α , β	D	Kidney (Ubiquitous)	Metabolic Disorders
GCNF	M/H	Testes, Ovary	Infertility
ERR α , β	M	Placenta, Bone	Infertility, Osteoporosis
FXR	D	Liver, Kidney	Metabolic Disorders
25 CAR α	H	Liver, Kidney	Metabolic Disorders
PXR	H	Liver, Intestine	Metabolic Disorders

30 The present invention thus provides methods for the treatment of NHR-associated conditions, comprising the step of administering to a subject in need thereof at least one compound of formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive

compounds in the present methods (for example, separately, or formulated together as a fixed dose). In the methods of the present invention, such other therapeutic agent(s) can be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

- 5 The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating a NHR-associated condition in an amount effective therefor, and a pharmaceutically acceptable carrier (vehicle or diluent). The compositions of the present invention can contain other therapeutic agents as described below, and can be formulated, for example, by
- 10 employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

It should be noted that the compounds of the present invention are, without limitation as to their mechanism of action, useful in treating any of the conditions or disorders listed or described herein such as inflammatory diseases or cancers, or other proliferate diseases, and in compositions for treating such conditions or disorders.

- The present compounds have therapeutic utility in the modulation of immune cell activation/proliferation, e.g., as competitive inhibitors of intercellular
- 20 ligand/receptor binding reactions involving CAMs (Cellular Adhesion Molecules) and Leukointegrins. For example, the present compounds modulate LFA-ICAM 1, and are particularly useful as LFA-ICAM 1 antagonists, and in the treatment of all conditions associated with LFA-ICAM 1 such as immunological disorders. Preferred utilities for the present compounds include, but are not limited to: inflammatory
- 25 conditions such as those resulting from a response of the non-specific immune system in a mammal (e.g., adult respiratory distress syndrome, shock, oxygen toxicity, multiple organ injury syndrome secondary to septicemia, multiple organ injury syndrome secondary to trauma, reperfusion injury of tissue due to cardiopulmonary bypass, myocardial infarction or use with thrombolytic agents, acute
- 30 glomerulonephritis, vasculitis, reactive arthritis, dermatosis with acute inflammatory components, stroke, thermal injury, hemodialysis, leukapheresis, ulcerative colitis, necrotizing enterocolitis and granulocyte transfusion associated syndrome) and

conditions resulting from a response of the specific immune system in a mammal (e.g., psoriasis, organ/tissue transplant rejection, graft vs. host reactions and autoimmune diseases including Raynaud's syndrome, autoimmune thyroiditis, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis, and systemic lupus erythematosus). The present compounds can be used in treating asthma or as an adjunct to minimize toxicity with cytokine therapy in the treatment of cancers. The present compounds can be employed in the treatment of all diseases currently treatable through steroid therapy. The present compounds may be employed for the treatment of these and other disorders alone or with other immunosuppressive or antiinflammatory agents. In accordance with the invention, a compound of the formula I can be administered prior to the onset of inflammation (so as to suppress an anticipated inflammation) or after the initiation of inflammation. When provided prophylactically, the immunosuppressive compound(s) are preferably provided in advance of any inflammatory response or symptom (for example, prior to, at, or shortly after the time of an organ or tissue transplant but in advance of any symptoms or organ rejection). The prophylactic administration of a compound of the formula I prevents or attenuates any subsequent inflammatory response (such as, for example, rejection of a transplanted organ or tissue, etc.) Administration of a compound of the formula I attenuates any actual inflammation (such as, for example, the rejection of a transplanted organ or tissue).

The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable

pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which
5 can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula I can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as
10 mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

5 Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound of the present invention can be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a adult human of from about 1 to 100 (for example, 15) mg/kg of body weight of 10 active compound per day, which can be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, 15 the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to NHR-associated conditions.

20 As mentioned above, the compounds of the present invention can be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of NHR-associated conditions.

For their preferred anticancer or antiangiogenic use, the compounds of the present invention can be administered either alone or in combination with other anti-cancer and cytotoxic agents and treatments useful in the treatment of cancer or other proliferative diseases, for example, where the second drug has the same or different mechanism of action than the present compounds of formula I. Examples of classes of anti-cancer and cytotoxic agents useful in combination with the present compounds include but are not limited to: alkylating agents such as nitrogen mustards, alkyl 25 sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes such 30

as L-asparaginase; farnesyl-protein transferase inhibitors; 5 α reductase inhibitors; inhibitors of 17 β -hydroxy steroid dehydrogenase type 3; hormonal agents such as glucocorticoids, estrogens/ antiestrogens, androgens/ antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, for example, paclitaxel (Taxol \circledR), docetaxel (Taxotere \circledR), and their analogs, and epothilones, such as epothilones A-F and their analogs; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and 10 miscellaneous agents such as hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators and monoclonal antibodies. The compounds of the invention may also be used in conjunction with 15 radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include but are not limited to mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, 20 fludarabine, pentostatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, etoposide phosphate, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, 25 buserelin, leuprolide, pteridines, diynes, levamisole, aflareon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethasone, gemicitabine hydrochloride, altretamine, and topotecan any analogs or derivatives thereof.

Preferred member of these classes include, but are not limited to, paclitaxel, 30 cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methotepatin, mitomycin C, ecteinascidin 743, or porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemicitabine, cytosine arabinoside, podophyllotoxin or

podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine and leurosine.

Examples of anticancer and other cytotoxic agents include the following:

- epothilone derivatives as found in German Patent No. 4138042.8; WO 97/19086, WO
5 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO
99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO
99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO
99/67252, WO 99/67253 and WO 00/00485; cyclin dependent kinase inhibitors as
found in WO 99/24416 (see also U.S. Patent No. 6,040,321); and prenyl-protein
10 transferase inhibitors as found in WO 97/30992 and WO 98/54966; and agents such
as those described generically and specifically in U.S. Patent No. 6,011,029 (the
compounds of which U.S. Patent can be employed together with any NHR modulators
(including, but not limited to, those of present invention) such as AR modulators, ER
modulators, with LHRH modulators, or with surgical castration, especially in the
15 treatment of cancer).

The combinations of the present invention can also be formulated or co-administered with other therapeutic agents that are selected for their particular usefulness in administering therapies associated with the aforementioned conditions. For example, the compounds of the invention may be formulated with agents to
20 prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H₁ and H₂ antihistaminics.

As it pertains to the treatment of cancer, the compounds of this invention are most preferably used alone or in combination with anti-cancer treatments such as radiation therapy and/or with cytostatic and/or cytotoxic agents, such as, but not
25 limited to, DNA interactive agents, such as cisplatin or doxorubicin; inhibitors of farnesyl protein transferase, such as those described in U.S. Patent No. 6,011,029; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors, such as CPT-11 or topotecan; tubulin stabilizing agents, such as paclitaxel, docetaxel, other taxanes, or epothilones; hormonal agents, such as tamoxifen; thymidilate synthase
30 inhibitors, such as 5-fluorouracil; antimetabolites, such as methotrexate; antiangiogenic agents, such as angiostatin, ZD6474, ZD6126 and comberstatin A2; kinase inhibitors, such as her2 specific antibodies, Iressa and CDK inhibitors; histone

deacetylase inhibitors, such as CI-994 and MS-27-275. Such compounds may also be combined with agents which suppress the production of circulating testosterone such as LHRH agonists or antagonists or with surgical castration.

For example, known therapies for advanced metastatic prostate cancer include
5 "complete androgen ablation therapy" wherein tumor growth is inhibited by controlling the supply of androgen to the prostate tissues via chemical castration (castration serves to inhibit the production of circulating testosterone (T) and dihydrotestosterone (DHT) followed by the administration of androgen receptor (AR) antagonists (which inhibit the function T/DHT derived from the conversion of
10 circulating androgen precursors to T/DHT by the prostate tissue). The compounds of the present invention can be employed as AR antagonists in complete ablation therapy, alone or in combination with other AR antagonists such as Flutamide, Casodex, Nilutamide, or Cyproterone acetate.

The compounds of the present invention may be employed adjuvant to
15 surgery.

Another application of the present compounds is in combination with antibody therapy such as but not limited to antibody therapy against PSCA. An additional application is in concert with vaccine / immune modulating agents for the treatment of cancer.

20 The above other therapeutic agents, when employed in combination with the compounds of the present invention, can be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The following assays can be employed in ascertaining the activity of a
25 compound as a NHR modulator. Preferred are those compounds with an activity greater than 20 μ m for binding or transactivation in any of these assays. Various compounds of the present invention were determined to have AR modulator activity utilizing the transactivation assay, and standard AR binding assays as described following.

Transactivation Assays:**AR Specific Assay:**

Compounds of the present invention were tested in transactivation assays of
5 a transfected reporter construct and using the endogenous androgen receptor of the
host cells. The transactivation assay provides a method for identifying functional
agonists and partial agonists that mimic, or antagonists that inhibit, the effect of native
hormones, in this case, dihydrotestosterone (DHT). This assay can be used to predict
10 *in vivo* activity as there is a good correlation in both series of data. See, e.g. T. Berger
et al., *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein
incorporated by reference.

For the transactivation assay a reporter plasmid is introduced by
transfection (a procedure to induce cells to take foreign genes) into the respective
cells. This reporter plasmid, comprising the cDNA for a reporter protein, such as
15 secreted alkaline phosphatase (SEAP), controlled by prostate specific antigen (PSA)
upstream sequences containing androgen response elements (AREs). This reporter
plasmid functions as a reporter for the transcription-modulating activity of the AR.
Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally
expressed by a gene under control of the AR and its native hormone. In order to
20 detect antagonists, the transactivation assay is carried out in the presence of constant
concentration of the natural AR hormone (DHT) known to induce a defined reporter
signal. Increasing concentrations of a suspected antagonist will decrease the reporter
signal (e.g., SEAP production). On the other hand, exposing the transfected cells to
increasing concentrations of a suspected agonist will increase the production of the
25 reporter signal.

For this assay, LNCaP and MDA 453 cells were obtained from the
American Type Culture Collection (Rockville, MD), and maintained in RPMI 1640 or
DMEM medium supplemented with 10% fetal bovine serum (FBS; Gibco)
respectively. The respective cells were transiently transfected by electroporation
30 according to the optimized procedure described by Heiser, 130 Methods Mol. Biol.,
117 (2000), with the pSEAP2/PSA540/Enhancer reporter plasmid. The reporter
plasmid, was constructed as follows: commercial human placental genomic DNA was

used to generate by Polymerase Cycle Reaction (PCR) a fragment containing the BglII site (position 5284) and the Hind III site at position 5831 of the human prostate specific antigen promoter (Accession # U37672), Schuur, et al., *J. Biol. Chem.*, **271** (12): 7043-51 (1996). This fragment was subcloned into the pSEAP2/basic

5 (Clontech) previously digested with BglII and HindIII to generate the pSEAP2/PSA540 construct. Then a fragment bearing the fragment of human PSA upstream sequence between positions -5322 and -3873 was amplified by PCR from human placental genomic DNA. A XhoI and a BglII sites were introduced with the primers. The resulting fragment was subcloned into pSEAP2/PSA540 digested with
10 XhoI and BglII respectively, to generate the pSEAP2/PSA540/Enhancer construct.
LNCaP and MDA 453 cells were collected in media containing 10% charcoal stripped FBS. Each cell suspension was distributed into two Gene Pulser Cuvetts (Bio-Rad) which then received 8 μ g of the reporter construct, and electroporated using a Bio-Rad Gene Pulser at 210 volts and 960 μ Faraday. Following the transfections the cells
15 were washed and incubated with media containing charcoal stripped fetal bovine serum in the absence (blank) or presence (control) of 1 nM dihydrotestosterone (DHT; Sigma Chemical) and in the presence or absence of the standard anti-androgen bicalutamide or compounds of the present invention in concentrations ranging from 10-10 to 10-5 M (sample). Duplicates were used for each sample. The compound
20 dilutions were performed on a Biomek 2000 laboratory workstation.

After 48 hours, a fraction of the supernatant was assayed for SEAP activity using the Phospha-Light Chemiluminescent Reporter Gene Assay System (Tropix, Inc). Viability of the remaining cells was determined using the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (MTS Assay, Promega). Briefly, a mix of a
25 tetrazolium compound (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; MTS) and an electron coupling reagent (phenazine methosulfate; PMS) are added to the cells. MTS (Owen's reagent) is bioreduced by cells into a formazan that is soluble in tissue culture medium, and therefore its absorbance at 490nm can be measured directly from 96 well assay plates
30 without additional processing. The quantity of formazan product as measured by the amount of 490nm absorbance is directly proportional to the number of living cells in culture. For each replicate the SEAP reading was normalized by the Abs490 value

derived from the MTS assay. For the antagonist mode, the % Inhibition was calculated as:

$$5 \quad \% \text{ Inhibition} = 100 \times (1 - [\text{average control} - \text{average blank} / \text{average sample} - \text{average blank}])$$

Data was plotted and the concentration of compound that inhibited 50% of the normalized SEAP was quantified (IC₅₀).

- 10 For the agonist mode % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

$$15 \quad \% \text{ Control} = 100 \times \text{average sample} - \text{average blank} / \text{average control} - \text{average blank}$$

Data was plotted and the concentration of compound that activates to levels 50% of the normalized SEAP for the control was quantified (EC₅₀).

GR Specificity Assay:

- 20 The reporter plasmid utilized was comprised of the cDNA for the reporter SEAP protein, as described for the AR specific transactivation assay. Expression of the reporter SEAP protein was controlled by the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequences that contains three hormone response elements (HREs) that can be regulated by both GR and PR see, e.g. G. Chalepakis et al., Cell, 53(3), 371 (1988). This plasmid was transfected into A549 cells, which expresses endogenous GR, to obtain a GR specific transactivation assay. A549 cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in RPMI 1640 supplemented with 10% fetal bovine serum (FBS; Gibco). Determination of the GR specific antagonist activity of the compounds of the present invention was identical to that described for the AR specific transactivation assay, except that the DHT was replaced with 5 nM dexamethasone (Sigma Chemicals), a specific agonist for GR. Determination of the GR specific agonist activity of the

compounds of the present invention was performed as described for the AR transactivation assay, wherein one measures the activation of the GR specific reporter system by the addition of a test compound, in the absence of a known GR specific agonists ligand.

5

PR Specific Assay:

The reporter plasmid utilized was comprised of the cDNA for the reporter SEAP protein, as described for the AR specific transactivation assay. Expression of the reporter SEAP protein was controlled by the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequences that contains three hormone response elements (HREs) that can be regulated by both GR and PR. This plasmid was transfected into T47D, which expresses endogenous PR, to obtain a PR specific transactivation assay. T47D cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS; Gibco). Determination of the PR specific antagonist activity of the compounds of the present invention was identical to that described for the AR specific transactivation assay, except that the DHT was replaced with 1 nM Promegestone (NEN), a specific agonist for PR. Determination of the PR specific agonist activity of the compounds of the present invention was performed as described for the AR transactivation assay, wherein one measures the activation of the PR specific reporter system by the addition of a test compound, in the absence of a known PR specific agonists ligand.

AR Binding Assay:

For the whole cell binding assay, human LNCaP cells (T877A mutant AR) or MDA 453 (wild type AR) in 96-well microtiter plates containing RPMI 1640 or DMEM supplemented with 10% charcoal stripped CA-FBS (Cocaleco Biologicals) respectively, were incubated at 37°C to remove any endogenous ligand that might be complexed with the receptor in the cells. After 48 hours, either a saturation analysis to determine the K_d for tritiated dihydrotestosterone, [3 H]-DHT, or a competitive binding assay to evaluate the ability of test compounds to compete with [3 H]-DHT were performed. For the saturation analysis, media (RPMI 1640 or DMEM – 0.2%

CA-FBS) containing [³H]-DHT (in concentrations ranging from 0.1 nM to 16 nM) in the absence (total binding) or presence (non-specific binding) of a 500-fold molar excess of unlabeled DHT were added to the cells. After 4 hours at 37°C, an aliquot of the total binding media at each concentration of [³H]-DHT was removed to estimate the amount of free [³H]-DHT. The remaining media was removed, cells were washed three times with PBS and harvested onto UniFilter GF/B plates (Packard), Microscint (Packard) was added and plates counted in a Top-Counter (Packard) to evaluate the amount of bound [³H]-DHT.

For the saturation analysis, the difference between the total binding and the non-specific binding, was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the K_d for [³H]-DHT. See e.g. D. Rodbard, Mathematics and statistics of ligand assays: an illustrated guide: In: J. Langon and J. J. Clapp, eds., Ligand Assay, Masson Publishing U.S.A., Inc., New York, pp. 45-99, (1981), the disclosure of which is herein incorporated by reference.

For the competition studies, media containing 1 nM [³H]-DHT and compounds of the invention ("test compounds") in concentrations ranging from 10^{-10} to 10^{-5} M were added to the cells. Two replicates were used for each sample. After 4 hours at 37°C, cells were washed, harvested and counted as described above. The data was plotted as the amount of [³H]-DHT (% of control in the absence of test compound) remaining over the range of the dose response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of [³H]-DHT bound in the absence of competing ligand was quantified (IC_{50}) after log-logit transformation. The K_I values were determined by application of the Cheng-Prusoff equation to the IC_{50} values, where:

$$K_I = \frac{IC_{50}}{(1 + [^3H\text{-DHT}] / K_d \text{ for } ^3\text{H-DHT})}$$

After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The K_d s for [³H]-DHT for MDA 453 and LNCaP were 0.7 and 0.2 nM respectively.

Human Prostate Cell Proliferation Assay:

Compounds of the present invention were tested ("test compounds") on the proliferation of human prostate cancer cell lines. For that, MDA PCa2b cells, a cell line derived from the metastasis of a patient that failed castration, Navone et al., *Clin. Cancer Res.*, 3, 2493-500 (1997), were incubated with or without the test compounds for 72 hours and the amount of [³H]-thymidine incorporated into DNA was quantified as a way to assess number of cells and therefore proliferation. The MDA PCa2b cell line was maintained in BRFF-HPC1 media (Biological Research Faculty & Facility 5 Inc., MD) supplemented with 10% FBS. For the assay, cells were plated in Biocoated 96-well microplates and incubated at 37°C in 10% FBS (charcoal-stripped)/BRFF-BMZERO (without androgens). After 24 hours, the cells were treated in the absence (blank) or presence of 1 nM DHT (control) or with test compounds (sample) of the 10 present invention in concentrations ranging from 10⁻¹⁰ to 10⁻⁵ M. Duplicates were 15 used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44 uCi. of [³H]-Thymidine (Amersham) was added per well and incubated for another 24 h followed by tripsinization, harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

20 The % Inhibition was calculated as:

$$\% \text{ Inhibition} = 100 \times (1 - [\text{average}_{\text{control}} - \text{average}_{\text{blank}} / \text{average}_{\text{sample}} - \text{average}_{\text{blank}}])$$

Data was plotted and the concentration of compound that inhibited 50% of the [³H]-Thymidine incorporation was quantified (IC₅₀).

C2C12 Mouse Myoblast Transactivation Assay:

Two functional transactivation assays were developed to assess the efficacy of androgen agonists in a muscle cell background using a luciferase reporter. The first assay (ARTA Stable 1) uses a cell line, Stable 1 (clone #72), which stably expresses the full length rat androgen receptor but requires the transient transfection of an 30 enhancer/reporter. This cell line was derived from C2C12 mouse myoblast cells. The second assay (ARTA Stable 2) uses a cell line, Stable 2 (clone #133), derived from Stable 1 which stably expresses both rAR and the enhancer/luciferase reporter.

The enhancer/reporter construct used in this system is pGL3/2XDR-1/luciferase. 2XDR-1 was reported to be an AR specific response element in CV-1 cells, Brown et. al. *The Journal of Biological Chemistry* 272, 8227-8235, (1997). It was developed by random mutagenesis of an AR/GR consensus enhancer sequence.

5

ARTA Stable 1:

1. Stable 1 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM 10 HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1X MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiotic-Antimycotic, and 800 µg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035).
2. 48 hours later, cells are transfected with pGL3/2XDR-1/luciferase using LipofectAMINE Plus™ Reagent (Gibco BRL, Cat. No.: 10964-013). 15 Specifically, 5 ng/well pGL3/2XDR-1/luciferase DNA and 50 ng/well Salmon Sperm DNA (as carrier) are diluted with 5 µl/well Opti-MEM media (Gibco BRL, Cat. No.: 31985-070). To this, 0.5 µl/well Plus reagent is added. This mixture is incubated for 15 minutes at room temperature. In a separate vessel, 0.385 µl/well LipofectAMINE reagent is diluted with 5 µl/well Opti-MEM. The 20 DNA mixture is then combined with the LipofectAMINE mixture and incubated for an additional 15 minutes at room temperature. During this time, the media from the cells is removed and replaced with 60 µl/well of Opti-MEM. To this is added 10 µl/well of the DNA/LipofectAMINE transfection mixture. The cells are incubated for 4 hours.
- 25 3. The transfection mixture is removed from the cells and replaced with 90 µl of media as in #1 above.
4. 10 µl/well of appropriate drug dilution is placed in each well.
5. 24 hours later, the Steady-Glo™ Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

30

ARTA stable 2

1. Stable 2 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM 5 HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1X MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiotic-Antimycotic, 800 μ g/ml Geneticin (Gibco BRL, Cat. No.: 10131-035) and 800 μ g/ml Hygromycin β (Gibco BRL, Cat. No.: 10687-010).
- 10 2. 48 hours later, the media on the cells is removed and replaced with 90 μ l fresh. 10 μ l/well of appropriate drug dilution is placed in each well.
- 15 3. 24 hours later, the Steady-GloTM Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

Proliferation Assays**15 Murine Breast Cell Proliferation Assay:**

The ability of compounds of the present invention ("test compounds") to modulate the function of the AR was determined by testing said compounds in a proliferation assay using the androgen responsive murine breast cell line derived from the Shionogi tumor, Hiraoka *et al.*, *Cancer Res.*, **47**, 6560-6564 (1987). Stable AR 20 dependent clones of the parental Shionogi line were established by passing tumor fragments under the general procedures originally described in Tetuo, *et. al.*, *Cancer Research* **25**, 1168-1175 (1965). From the above procedure, one stable line, SC114, was isolated, characterized and utilized for the testing of example compounds. SC114 cells were incubated with or without the test compounds for 72 hours and the amount 25 of [³H]-thymidine incorporated into DNA was quantified as a surrogate endpoint to assess the number of cells and therefore the proliferation rate as described in Suzuki *et. al.*, *J. Steroid Biochem. Mol. Biol.* **37**, 559-567 (1990). The SC114 cell line was maintained in MEM containing 10⁻⁸ M testosterone and 2% DCC-treated FCS. For the assay, cells were plated in 96-well microplates in the maintenance media and 30 incubated at 37°C. On the following day, the medium was changed to serum free medium [Ham's F-12:MEM (1;1, v/v) containing 0.1% BSA] with (antagonist mode) or without (agonist mode) 10⁻⁸ M testosterone and the test compounds of the present

invention in concentrations ranging from 10^{-10} to 10^{-5} M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44uCi of [³H]-Thymidine (Amersham) was added per well and incubated for another 2 hr followed by trypsinization, and

- 5 harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

For the antagonist mode, the % Inhibition was calculated as:

$$\% \text{ Inhibition} = 100 \times (1 - [\text{average sample} - \text{average blank}] / \text{average control} - \text{average blank})$$

10)

Data was plotted and the concentration of compound that inhibited 50% of the [³H]-Thymidine incorporation was quantified (IC₅₀).

- 15 For the agonist mode % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

$$\% \text{ Control} = 100 \times (\text{average sample} - \text{average blank}) / (\text{average control} - \text{average blank})$$

20

Data was plotted and the concentration of compound that inhibited 50% of the [³H]-Thymidine incorporation was quantified (EC₅₀).

In Vitro Assay to Measure GR Induced AP-1 Transrepression:

- 25 The AP-1 assay is a cell based luciferase reporter assay. A549 cells, which contain endogenous glucocorticoid receptor, were stably transfected with an AP-1 DNA binding site attached to the luciferase gene. Cells are then grown in RPMI + 10% fetal calf serum (charcoal-treated) + Penicillin/Streptomycin with 0.5mg/ml geneticin. Cells are plated the day
- 30 before the assay at approximately 40000 cells/well. On assay day, the media is removed by aspiration and 20 μ l assay buffer (RPMI without phenol red + 10% FCS (charcoal-treated) + Pen/Strep) is added to each

well. At this point either 20 μ l assay buffer (control experiments), the compounds of the present invention ("test compounds") (dissolved in DMSO and added at varying concentrations) or dexamethasone (100 nM in DMSO, positive control) are added to each well. The plates are then 5 pre-incubated for 15 minutes at 37°C, followed by stimulation of the cells with 10 ng/ml PMA. The plates are then incubated for 7 hrs at 37°C after which 40 μ l luciferase substrate reagent is added to each well. Activity is measured by analysis in a luminometer as compared to control experiments treated with buffer or dexamethasone. Activity is 10 designated as % inhibition of the reporter system as compared to the buffer control with 10 ng/ml PMA alone. The control, dexamethasone, at a concentration of \leq 10 μ M typically suppresses activity by 65%. Test compounds which demonstrate an inhibition of PMA induction of 50% or greater at a concentration of test compound of \leq 10 μ M are deemed active.

15

Wet Prostate Weight Assay AR Antagonist Assay:

The activity of compounds of the present invention as AR antagonists was investigated in an immature male rat model, a standard, recognized test of antiandrogen activity of a given compound, as described in L. G. Hershberger et al.,

20 *Proc. Soc. Expt. Biol.*, **83**, 175 (1953); P. C. Walsh and R. F. Gittes, "Inhibition of extratesticular stimuli to prostate growth in the castrated rat by antiandrogens", *Endocrinology*, **86**, 624 (1970); and B. J. Furr et al., "ICI 176,334: A novel non-steroid, peripherally selective antiandrogen", *J. Endocrinol.*, **113**, R7-9 (1987), the disclosures of which are herein incorporated by reference.

25

The basis of this assay is the fact that male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the 30 pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within

the prostate by 5 α -reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men. F. Labrie et al. Clin. Invest. Med., 16, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the 5 prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues. M. C. Luke and D. S. Coffey, "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435-1487 (1994). Since the male sex organs are the tissues most responsive to modulation of the androgen activity, this model is used to determine the 10 androgen dependent growth of the sex accessory organs in immature castrated rats.

Male immature rats (19-20 days old Sprague-Dawley, Harlan Sprague-Dawley) were castrated under metofane anestesia. Five days after surgery these castrated rats (60-70g, 23-25 day-old) were dosed for 3 days. Animals were dosed sub-cutaneously (s.c.) 1mg/kg with Testosterone Propionate (TP) in arachis oil 15 vehicle and anti-androgen test compounds (compounds of the present invention) were dosed orally by gavage (p.o.) in dissolved/suspensions of 80% PEG 400 and 20% Tween 80 (PEGTW). Animals were dosed (v/w) at 0.5 ml of vehicle /100g body weight. Experimental groups were as follows:

1. Control vehicle
- 20 2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD), a recognized antiandrogen, as a reference compound.
4. To demonstrate antagonist activity, a compound of the present invention ("test compound") was administered (p.o. in PEGTW, QD) with TP (s.c. as 25 administered in group 2) in a range of doses.
5. To demonstrate agonist activity a compound of the present invention ("test compound") was administered alone (p.o. in PEGTW, QD) in a range of doses.

At the end of the 3-day treatment, the animals were sacrificed, and the 30 ventral prostate weighed. To compare data from different experiments, the sexual organs weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase

(100%). ANOVA followed by one-tailed Student or Fischer's exact test was used for statistical analysis.

The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., *J. Urol.*, **145**, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In immature castrated rats, replacement of exogenous androgens increases seminal vesicles (SV) and the ventral prostate (VP) in a dose dependent manner.

10 The maximum increase in organ weight was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC₅₀ of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher 15 serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

20 In this immature castrated rat model, a known AR antagonist (Casodex) was also administered simultaneously with 0.1 mg of TP (ED₅₀), inhibiting the testosterone-mediated increase in the weights of the VP and SV in a dose dependent manner. The antagonist effects were similar when dosing orally or subcutaneously. Compounds of the invention also exhibited AR antagonist activity by suppressing the 25 testosterone-mediated increase in the weights of VP and SV.

25

Levator Ani & Wet Prostate Weight Assay AR Agonist Assay:

The activity of compounds of the present invention as AR agonists was investigated in an immature male rat model, a recognized test of anabolic effects in muscle and sustaining effects in sex organs for a given compound, as described in L. 30 G. Hershberger et al., *Proc. Soc. Expt. Biol. Med.*, **83**, 175 (1953); B. L. Beyler et al, "Methods for evaluating anabolic and catabolic agents in laboratory animals", *J. Amer. Med. Women's Ass.*, **23**, 708 (1968); H. Fukuda et al., "Investigations of the

levator ani muscle as an anabolic steroid assay", *Nago Dai. Yak. Ken. Nem.* **14**, 84 (1966) the disclosures of which are herein incorporated by reference.

The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man. Androgenic steroids, such as testosterone (T), have been well characterized for their ability to maintain muscle mass. Treatment of animals or humans after castrations with an exogenous source of T results in a reversal of muscular atrophy. The effects of T on muscular atrophy in the rat levator ani muscle have been well characterized, M. Masuoka et al., "Constant cell population in normal, testosterone deprived and testosterone stimulated levator ani muscles" *Am. J. Anat.* **119**, 263 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. I. Quantitative data" *Boll. -Soc. Ital. Biol. Sper.* **42**, 1596 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. II. Electron-microscopic observations" *Boll. -Soc. Ital. Biol. Sper.* **42**, 1600 (1966); A. Boris et al., *Steroids* **15**, 61 (1970). As described above, the effects of androgens on maintenance of male sexual accessory organs, such as the prostate and seminal vesicles, is well described. Castration results in rapid involution and atrophy of the prostate and seminal vesicles. This effect can be reversed by exogenous addition of androgens. Since both the levator ani muscle and the male sex organs are the tissues most responsive to the effects of androgenic agents, this model is used to determine the androgen dependent reversal of atrophy in the levator ani muscle and the sex accessory organs in immature castrated rats. Sexually mature rats (200-250 g, 6-8 weeks-old, Sprague-Dawley, Harlan) were acquired castrated from the vendor (Taconic). The rats were divided into groups and treated daily for 7 to 14 days with one of the following:

1. Control vehicle
2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD), a recognized antiandrogen, as a reference compound.
4. To demonstrate antagonist activity, a compound of the present invention ("test compound") was administered (p.o. in PEGTW, QD) with TP (s.c. as administered in group 2) in a range of doses.

5. To demonstrate agonist activity a compound of the present invention ("test compound") was administered alone (p.o. in PEGTW, QD) in a range of doses.

At the end of the 7-14-day treatment, the animals were sacrificed by carbon dioxide, and the levator ani, seminal vesicle and ventral prostate weighed. To compare data from different experiments, the levator ani muscle and sexual organ weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%).

Super-anova (one factor) was used for statistical analysis.

10 The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., *J. Urol.*, **145**, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen 15 antagonist. In immature castrated rats, replacement of exogenous androgens increases levator ani, seminal vesicles (SV) and prostate in a dose dependent manner.

15 The maximum increase in organ weight was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC₅₀ of T and TP were about 1 mg and 0.03 mg, respectively. The 20 increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 25 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

MDA PCa2b Human Prostate Zenograft Assay:

30 *In Vivo* Antitumor Testing: MDA-PCa-2b human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in adult male nude mice (4-6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5-6 weeks.

For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors were allowed to grow to approx. 100-200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula: $\text{Tumor weight} = (\text{length} \times \text{width}^2) \div 2$.

Tumor response end-point was expressed in terms of tumor growth inhibition (%T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

$\text{TVDT} = \text{Median time (days) for control tumors to reach target size} - \text{Median time (days) for control tumors to reach half the target size}$
And, $\text{Log cell kill} = (T-C) \div (3.32 \times \text{TVDT})$.

Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

25

Dunning Prostate Tumor:

Dunning R3327H prostate tumor is a spontaneously derived, well differentiated androgen responsive adenocarcinoma of the prostate (Smolev JK, Heston WD, Scott WW, and Coffey DS, *Cancer Treat Rep.* **61**, 273-287 (1977)). The growth of the R3327H subline has been selected for its highly androgen-dependent and reproducible growth in intact male rats. Therefore, this model and other sublines of this tumor have been

widely used to evaluate *in vivo* antitumor activities of antiandrogens such as flutamide and bicalutamide/Casodex (Maucher A., and von Angerer, *J. Cancer Res. Clin. Oncol.*, **119**, 669-674 (1993), Furr B.J.A. *Euro. URL.* **18** (suppl. 3), 2-9 (1990), Shain S.A. and Huot RI. *J. Steriod Biochem.* **31**,

5 711-718 (1988)).

At the beginning of the study, the Dunning tumor pieces (about 4 x 4 mm) are transplanted subcutaneously to the flank of mature male Copenhagen rats (6-7 weeks old, Harlan-Sprague Dawley, Indianapolis, MD). About 6 weeks after the implantation, the animals with tumors of

10 measurable size (about 80 - 120 mm³) are randomized into treatment groups (8-10 rats/group) and the treatments are initiated. One group of the rats are castrated to serve as the negative control of tumor growth. Animals are treated daily with compounds of the current invention, standard antiandrogens such as bicalutamide or vehicle (control) for an 15 average of 10 to 14 weeks. Test compounds are dissolved in a vehicle of (2.5 ml/kg of body weight) 10% polyethylene glycol and 0.05% Tween-80 in 1% carboxymethyl cellulose, PEG/CMC, (Sigma, St Louis, MO). Typical therapeutic experiments would include three groups of three escalating doses for each standard or test compound (in a range of 300-3 mg/kg).

20 Tumors in the vehicle (control) group reach a size of 1500 to 2500 mm³, whereas the castrated animal group typically shows tumor stasis over the 14 weeks of observation. Animals treated orally with 20 mg/kg of bicalutamide or flutamide would be expected to show a 40% reduction in tumor volumes compared to control after 14 weeks of treatment. The size of tumors are measured weekly by vernier 25 caliper (Froboz, Switzerland), taking perpendicular measurements of length and width. Tumor volumes are measured in mm³ using the formula: Length x Width x Height = Volume. Statistical differences between treatment groups and control are evaluated using multiple ANOVA analysis followed by one tail non-parametric Student t test.

Mature Rat Prostate Weight Assay:

The activity of compounds of the present invention were investigated in a mature male rat model, which is a variation of the Levator ani & wet prostate weight assay described above. The above *in vivo* assays are recognized assays for
5 determining the anabolic effects in muscle and sustaining effects in sex organs for a given compound, as described in L. G. Hershberger *et al.*, 83 *Proc. Soc. Expt. Biol. Med.*, 175 (1953); B. L. Beyler *et al.*, "Methods for evaluating anabolic and catabolic agents in laboratory animals", 23 *J. Amer. Med. Women's Ass.*, 708 (1968); H. Fukuda *et al.*, "Investigations of the levator ani muscle as an anabolic steroid assay", 14 *Nago*
10 *Dai. Yak. Ken. Nem.* 84 (1966) the disclosures of which are herein incorporated by reference. The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man.

The male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by 5 α -reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men. F. Labrie *et. al.* 16 *Clin. Invest. Med.*, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles
20 without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues, M. C. Luke and D. S. Coffey, "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435-1487 (1994). Since the male sex organs and the levator ani are the tissues most responsive to modulation of the androgen activity, this model is used to determine the
25 activity of compounds that modulate the androgen receptor pathway in mature rats.

Along with its mitogenic activity on tissues such as prostate, seminal vesicle and muscle, testosterone also serves as a negative regulator for its own

biosynthesis. Testosterone production in the Leydig cells of the testis is controlled by the level of circulating LH released from the pituitary gland. LH levels are themselves controlled by the level of LHRH produced in the hypothalmic region.

Testosterone levels in the blood serve to inhibit the secretion of LHRH and 5 subsequently reduce levels of LH and ultimately the levels of circulating testosterone levels. By measuring blood levels of LH as they are effected by compounds of the present invention ("test compounds"), it is possible to determine the level of agonist or antagonist activity of said compounds at the hypothalamic axis of this endocrine cycle.

10 Matched sets of Harlan Sprague-Dawely rats (40-42 days old, 180-220 g), were dosed orally by gavage (p.o.) with the test compounds in dissolved/suspensions of 80% PEG 400 and 20% Tween 20 (PEGTW) for 14 days. Two control groups, one intact and one castrated were dose orally only with the PEGTW vehicle. Animals were dosed (v/w) at 0.5 ml of vehicle /100g body weight. Experimental groups were 15 as follows:

1. Intact vehicle (p.o., PEGTW, QD)
2. Control vehicle (p.o., PEGTW, QD)
3. Bicalutamide (Casodex, a recognized antiandrogen, as a reference compound) or a compound of the present invention, p.o. in PEGTW QD. (in a range of doses).

20 At the end of the 14-day treatment, the animals were sacrificed, and the ventral prostate, the seminal vesicles, and the levator ani were removed surgically and weighed. To compare data from different experiments, the organs weights were first standardized as mg per 100 g of body weight, and expressed as a percentage of the value of the respective organ in the intact group.

25 Rat luteinizing hormone (rLH) is quantitatively determined with the Biotrak [125 I] kit (Amersham Pharmacia Biotek), following the manufacturer directions. The assay is based on the competition by the LH present in the serum of the binding of [¹²⁵I] rLH to an Amerlex-M bead/antibody suspension. The radioactivity that remains after incubation with the serum and subsequent washes is extrapolated into a 30 standard curve to obtain a reading in ng/ml.

The gain and loss of sexual organ and levator ani weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the

serum androgen concentration, see Y. Okuda *et al.*, *J. Urol.*, **145**, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In the mature rats assay, active agonist agents will have no effect or will

5 increase the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a suppressive effect on LH secretion. Compounds with antagonist activity will decrease the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a reduced suppressive effect on LH secretion.

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CWR22 Human Prostate Zenograft Assay:

In Vivo Antitumor Testing: CWR22 human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in 5 adult male nude mice (4-6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5-6 weeks.

For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) 10 with a 13-gauge trocar. Tumors were allowed to grow to approx. 100-200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of 15 animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size 20 of 0.5 gm. Tumor weights (mg) were estimated from the formula: Tumor weight = (length x width²) ÷ 2.

Tumor response end-point was expressed in terms of tumor growth inhibition (%T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

25 To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

TVDT = Median time (days) for control tumors to reach target size – Median time (days) for control tumors to reach half the target size

And, Log cell kill = (T-C) ÷ (3.32 x TVDT)

30 Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims.

Abbreviations

- 5 The following abbreviations are used herein:
- 4-DMAP = 4-dimethylaminopyridine
DMF = dimethylformamide
EtOAc = ethyl acetate
Me = methyl
- 10 RT = retention time
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
pTSA = para-toluenesulfonic acid
- 15 Δ = heat
t-Bu = *tert*-butyl
TMSOTf = trimethylsilyl trifluoromethane sulfonate
TEA = triethylamine
n-BuLi = *n*-butyllithium
- 20 rt = room temperature
LC = liquid chromatography
Ph = phenyl
Et = ethyl
DMS = dimethylsulfate
- 25 MS = molecular sieves
MS(ES) = Electro-Spray Mass Spectrometry
mCPBA = m-chloroperoxybenzoic acid
sat = saturated
Ac = acetyl
- 30 h = hours
HMPA = hexamethylphosphoramide
Lawesson's Reagent = 2,4-bis(4-methoxyphenyl)-1,3,2,4-

dithiadiphosphetane-2,4-disulfide

Freshyl cracked cyclopentadiene = monomer of cyclopentadiene

generated by Diels-Alder dimer product

AIBN = 2,2'-azobis(2-methylpropionitrile)

5

aq = aqueous

QD = dosed once a day

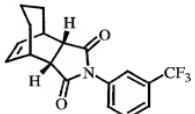
PMA = Phrobal-12-myristate-13 acetate

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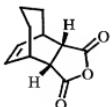
Example 1

(3a α ,4 β ,8 β ,8a α)-4,5,6,7,8,8a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione (1B)

5



A. (3a α ,4 β ,8 β ,8a α)-4,5,6,7,8,8a-Hexahydro-4,8-etheno-1H-cyclohepta[c]furan-1,3(3aH)-dione (1A)



10 Compound 1A was made in accordance with the procedure described in Kohler, *et. al.*, *J. Am. Chem. Soc.* 1057-1061 (1939). A solution of cycloheptadiene (5 g, 53.1 mmol, 1 eq) and maleic anhydride (5.73 g, 58.4 mmol, 1.1 eq) in xylenes (300 mL) was heated to reflux overnight. The solution was concentrated via distillation and hexanes 15 were added until the solution became cloudy. The resulting brown precipitate (~1 g) was removed by filtration and the filtrate were placed in a freezer. The white solid which crystallized from the filtrate was isolated by filtration and dried under vacuum to give 5 g of compound 1A which required no further purification.

20

B. (3a α ,4 β ,8 β ,8a α)-4,5,6,7,8,8a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione (1B)

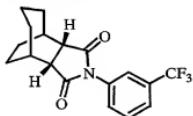
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Compound **1A** (100 mg, 0.520 mmol, 1.2 eq) was combined with 3-(trifluoromethyl)aniline (0.054 mL, 0.434 mmol, 1 eq) in acetic acid (2 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was isolated by 5 filtration. The material was washed sequentially with aqueous K_2CO_3 and water and then dried in a vacuum oven to provide 114.2 mg (78.4%) of compound **1B** as a tan crystalline solid. HPLC: 98% at 1.82 min (retention time) (YMC S5 TurboPack Pro column 4.6 x 33 mm, 10-90% aqueous methanol over 2 minutes containing 0.1% $\text{CF}_3\text{CO}_2\text{H}$, 4 mL/min, monitoring 10 at 220 nm), MS (ES): m/z 336.2 [M+ H]⁺.

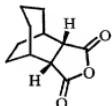
Example 2

(3 α o,4 β ,8 β ,8 α o)-4,5,6,7,8,8a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,8-ethanocyclohepta[c]pyrrole-

1,3(2H,3aH)-dione (2B)



A. (3 α o,4 β ,8 β ,8 α o)-4,5,6,7,8,8a-Hexahydro-4,8-ethano-1H-cyclohepta[c]furan-1,3(3aH)-dione (2A)



20 A solution of compound **1A** (1 g, 5.20 mmol) and 10% Pd/C (~20 mg) in EtOAc was shaken under H_2 at 40 psi overnight. The reaction solution was filtered through a pad of celite eluting with EtOAc and concentrated to give 0.86 g of compound **2A** as a white powder.

B. (3,8*α*,4β,8β,8*α*)-4,5,6,7,8*a*-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,8*α*ethanocyclohepta[c]pyrrole-1,3(2H,3aH)-dione (2B)

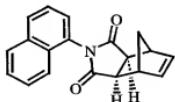
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Compound **2A** (2.37 g, 12.2 mmol, 1.2 eq) was combined with (trifluoromethyl)aniline (1.27 mL, 10.2 mmol, 1.0 eq) in AcOH (45 mL) and heated at 115 °C ovt. night. After the reaction mixture was cooled to room temperature, the resulting precipitate was collected, washed with MeOH and dried to give 2.7 g 10 (78.6%) of compound **2B** as a white crystalline solid. HPLC: 99% at 3.61 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm), MS (ES): 34/z 338.4 [M+H]⁺.

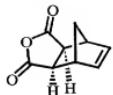
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Example 3

(3*α*β,4*β*,7*β*,7*α*)-3*α*,4,7,7*a*-Tetrahydro-2-(1-naphthalenyl)-4,7-10*n* methano-1*H*-isoindole-1,3(2*H*)-dione (3B)



20 **A. *cis*-5-Norbornene-*exo*-2,3-dicarboxylic anhydride (3A)**



Compound **3A** was made in accordance with the procedure described in Norman *et. al.*, US Patent No. 3,995,099. *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (4 g) was heated for 4 hours at 220 °C. The resuming solid was recrystallized 4X from benzene to give 0.63 g of compound **3A** (>99:1 *exo* by ¹H NMR) as light brown crystals.

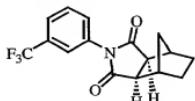
B. (3 α ,4 β ,7 β ,7 α)-3a,4,7,7a-Tetrahydro-2-(1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (3B)

5 Compound **3A** (100 mg, 0.609 mmol, 1.1 eq) was combined with 1-aminonaphthalene (79 mg, 0.554 mmol, 1 eq) in acetic acid (2 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was isolated by filtration. The material was washed sequentially with aqueous K_2CO_3 and water. Treatment with charcoal to remove colored
10 impurities, followed by drying under vacuum provided 103.2 mg (64.7%) of compound **3B** as an off-white powder. HPLC: 95% at 1.54 min (retention time) (YMC S5 TurboPack Pro column 4.6 x 33 mm, 10-90% aqueous methanol over 2 minutes containing 0.1% CF_3CO_2H , 4 mL/min, monitoring at 220 nm), MS (ES): m/z 290.0 [M+H]⁺.

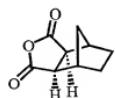
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Example 4

(3 α ,4 β ,7 β ,7 α)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione (4B)



20 A. **(3 α ,4 β ,7 β ,7 α)-Hexahydro-4,7-methanobenzofuran-1,3-dione (4A)**



25 A solution of compound **3A** (434 mg, 2.64 mmol) and 10% Pd/C (~10 mg) in EtOAc was stirred under H_2 balloon overnight. The reaction

mixture was filtered through celite eluting with EtOAc, concentrated under reduced pressure to give 429 mg of compound **4A** as an off-white powder.

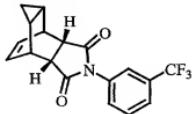
5 **B. (3a α ,4 β ,7 β ,7a α)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione (4B)**

Compound **4A** (1.8 g, 10.84 mmol, 1.0 eq) was combined with 3-(trifluoromethyl)aniline (1.49 mL, 11.93 mmol, 1.1 eq) in AcOH (40 mL) and heated 10 at 115 °C overnight. After the reaction mixture was cooled to room temperature, the resulting precipitate was collected, washed with MeOH and recrystallized from CH₂Cl₂/hexanes to give 2.17 g (64.8%) of compound **4B** as a white crystalline solid. HPLC: 99% at 3.23 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, 15 monitoring at 220 nm), MS (ES): m/z 310.2 [M+H]⁺.

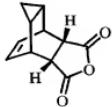
Example 5

(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-ethenocycloprop[*f*]isoindole-

20 1,3(2H,3aH)-dione (5B)



A. **(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-4,6-etheno-1H-cycloprop[*f*]isobenzofuran-1,3(3aH)-dione (5A)**



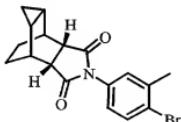
Compound **5A** was made in accordance with the procedure described in Schueler *et. al.*, *J. Org. Chem.* **39**, 2063-2069 (1974). A solution of cycloheptatriene (6.1 mL, 58.79 mmol, 1.1 eq) and maleic anhydride (5.1 g, 53.44 mmol, 1.0 eq) in xylenes (20 mL) was heated to reflux for 90 hours. The reaction mixture was placed in the freezer, and the resulting precipitate was filtered, washed with xylenes and dried to give 4.10 g compound **5A** as a white crystalline solid.

B. (3a ω 4 β ,4a ω ,5a ω ,6 β ,6a ω)-4,4a β ,5,5a,6,6a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)-dione (5B)

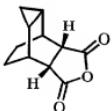
Compound **5A** (100 mg, 0.526 mmol, 1.2 eq) was combined with 3-(trifluoromethyl)aniline (0.055 mL, 0.438 mmol, 1 eq) in acetic acid (2 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was isolated by filtration. The material was washed sequentially with aqueous K_2CO_3 and water and then dried in a vacuum oven to provide 145.5 mg (99%) of compound **5B** as an off-white crystalline solid. HPLC: 99% at 1.74 min (retention time) (YMC S5 TurboPack Pro column 4.6 x 33 mm, 10-20% aqueous methanol over 2 minutes containing 0.1% CF_3CO_2H , 4 mL/min, monitoring at 220 nm), MS (ES): m/z 334.0 [M+H]⁺.

Example 6

(3ac,4B,4ac,5ac,6B,6ac)-2-(4-Bromo-3-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[flisoindole-1,3(2H,3aH)-dione (6B)

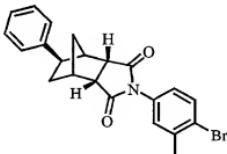


A. (3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-Hexahydro-4,6-ethano-1H-cycloprop[f]isobenzofuran-1,3(3aH)-dione (6A)

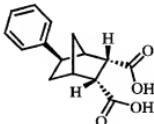


- 5 Compound **6A** was made in accordance with the procedure described in Ishitobi *et al*, *Bull. Chem. Soc. Japan* **44**, 2993-3000 (1971). A solution of compound **5A** (10 g, 52.58 mmol) and 10% Pd/C (0.6 g) in 15:1 acetic acid:acetic anhydride (176 mL) was stirred under H₂ balloon until starting material was consumed (~ 1 h). The reaction mixture was 10 filtered through celite, eluting with EtOAc and concentrated under reduced pressure. The resulting oil was triturated with hexanes and the solid was recrystallized from toluene/hexanes to give 8 g compound **6A** as a white crystalline solid.
- 15 **B. (3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(4-Bromo-3-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione (6B)**

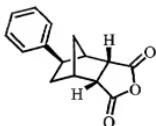
20 Compound **6A** (1.92 g, 10 mmol, 1.0 eq) was combined with 4-bromo-3-methylaniline (2.05 g, 11 mmol, 1.1 eq) in AcOH (40 mL) and heated at 115 °C overnight. After the reaction mixture was cooled to room temperature, the resulting precipitate was collected, washed with MeOH and dried to give 3.2 g (88.9%) of compound **6B** as a white crystalline solid. HPLC: 99% at 3.52 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 360.0 & 362.0 [M+H]⁺.

Example 7**(3 α ,4 α ,5 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)hexahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (7C)**

- 5 A. (2-endo, 3-endo, 5-exo)-5-Phenylbicyclo[2.2.1]heptane-2,3-dicarboxylic acid (7A)



- Compound 7A was made in accordance with the procedure
10 described in Stájer *et. al.*, *Acta. Chem. Scand.* **50**, 922-30 (1996). To a suspension of aluminum trichloride (11.5 g, 86.0 mmol, 2.4 eq) in benzene (20 mL) was added *cis*-norbornene-*endo*-2,3-dicarboxylic acid (6.53 g). After stirring for 30 min, the reaction mixture was heated to 50 °C for 2 hours. The cooled reaction mixture was poured onto ice (170 mL) and 15 conc. HCl (17 mL) and the resulting precipitate was filtered, washed with cold H₂O and dried. Recrystallization of the solid from glacial acetic acid gave 7.73 g of compound 7A as a white solid, which was taken on without further purification.
- 20 B. (3 α ,4 α ,5 α ,7 α ,7a α)-Hexahydro-5-phenyl-4,7-methanoisobenzofuran-1,3-dione (7B)



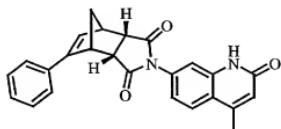
A solution of compound **7A** (7.7 g, 29.6 mmol) in Ac₂O (30 mL) was heated to reflux for 3 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 50% EtOAc/hexanes, to give 5.2 g of compound **7B** as a tan viscous oil, which solidified on standing.

10 **C. (3 α ,4 α ,5 α ,7 α ,7 α)-2-(4-Bromo-3-methylphenyl)hexahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (7C)**

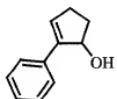
Compound **7B** (1 g, 4.13 mmol, 1 eq) was combined with 4-bromo-3-methylaniline (768 mg, 4.13 mmol, 1 eq) in acetic acid (20 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added and the reaction was extracted with CH₂Cl₂. The organic extracts were washed with aqueous NaHCO₃, dried over MgSO₄, concentrated *in vacuo*, and purified by flash chromatography on silica gel eluting with a gradient of 25-50% ethyl acetate in hexanes to provide 1.6 g (95%) of compound **7C** as a light yellow crystalline solid. HPLC: 99% at 3.96 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-20% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 410.0 & 412.0 [M+H]⁺.

Example 8

(3 α ,4 α ,7 α ,7 α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)-3 α ,4,7,7a-tetrahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (8C)

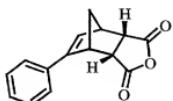


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A. 2-Phenyl-2-cyclopenten-1-ol (8A)

Compound **8A** was made in accordance with the procedure
 10 described in Hart, *et. al.*, *Tetrahedron Lett.* **29**, 881-884 (1988). To a
 solution of 1-phenylcyclopentene (5 g, 34.67 mmol, 1 eq) in *t*-BuOH (87
 mL) was added selenium dioxide (4.2 g, 38.14 mmol, 1.1 eq). After stirring
 overnight, the reaction mixture was filtered through celite and
 concentrated under reduced pressure. The crude material was purified by
 15 flash chromatography on silica gel eluting with 25% EtOAc/hexanes to
 give 2.6 g of compound **8A**.

B. (3 α ,4 α ,7 α ,7 α)-3 α ,4,7,7a-Tetrahydro-5-phenyl-4,7-methanoisobenzofuran-1,3-dione (8B)



20

A mixture of compound **8A** (1.3 g, 8.11 mmol, 1 eq), maleic
 anhydride (796 mg, 8.11 mmol, 1 eq) and CuSO₄ (2.6 g, 16.23 mmol, 2 eq)

in benzene (50 mL) was heated to reflux overnight. The cooled reaction solution was poured into H₂O and the resulting mixture was extracted with EtOAc (3X), dried over MgSO₄ and purified by flash chromatography on silica gel eluting with 25% EtOAc/Hexanes to give 1.13 g of compound

5 **8B** as a light tan powder.

C. (3a α ,4 α ,7a α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)-3a,4,7,7a-tetrahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (8C)

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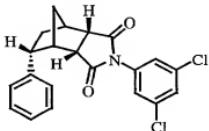
Compound **8B** (60 mg, 0.25 mmol, 1.0 eq) was combined with 7-amino-4-methyl-2(1H)-quinoline (47.9 mg, 0.27 mmol, 1.1 eq) in AcOH (1.5 mL) and heated at 115 °C overnight. The reaction mixture was concentrated under reduced pressure.

Purification by flash chromatography on SiO₂ eluting with a gradient of 0% to 10% 15 methanol/EtOAc followed by recrystallization from AcOH/H₂O gave 31.4 mg (32%) of compound **8C** as a light tan solid. HPLC: 95% at 3.14 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 397.0 [M+H]⁺.

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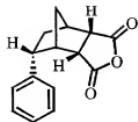
Example 9

(3a α ,4 α ,5 β ,7a α)-2-(3,5-Dichlorophenyl)hexahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (9B)



25

A. (3a α ,4 α ,5 β ,7a α)-hexahydro-5-phenyl-4,7-methanoisobenzofuran-1,3-dione (9A)



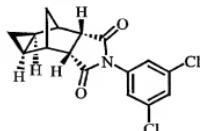
Compound **8B** (0.66 g, 2.75 mmol) was reduced with 10% Pd/C in EtOAc (14 mL) under H₂ at 50 psi. When the pressure on gauge remained 5 constant, the reaction mixture was filtered through celite and concentrated under reduced pressure to give 0.61 g compound **9A** as a yellow oil.

- 10 B. (3a α ,4 α ,5 β ,7 α ,7a α)-2-(3,5-Dichlorophenyl)hexahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione (**9B**)

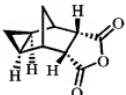
Compound **9A** (50 mg, 0.21 mmol, 1.2 eq) was combined with 3,5-dichloroaniline (28 mg, 0.17 mmol, 1 eq) in acetic acid (1 mL) and heated at 121 °C overnight. The reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 5% ethyl acetate in CH₂Cl₂ to provide 11.2 mg (17.1%) of compound **9B** as a beige solid. HPLC: 90% at 3.87 min (retention time) (YMC ODSA S5 C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% CF₃CO₂H, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 20 386.0 & 388.0 [M+H]⁺.

Example 10

- (3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-2-(3,5-Dichlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-methanocyclopropylisoindole-1,3(2H,3aH)-dione (**10B**)



A. (3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-4,4a,5,5a,6,6a-Hexahydro-4,6-methano-1H-cycloprop[f]isobenzofuran-1,3(3aH)-dione (10A)



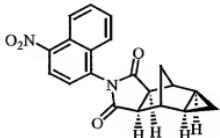
Compound 10A was made in accordance with the procedure described in Kato, *et. al.*, *Synthesis*, 636-637 (1995), Creary, *et. al.*, *J. Org. Chem.* **40**, 3326-3331 (1975) and Fieser & Fieser coll. vol. 1, pg. 192. A mixture of 40% aq. KOH (23 mL) and Et₂O (75 mL) was cooled to 0 °C. N-Methyl-N'-nitro-N-nitrosoguanidine (7.5 g) was added portionwise to the mixture and stirred for 5 min. The Et₂O layer was separated and added dropwise to a stirred solution of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (3 g, 18.3 mmol) and Pd(OAc)₂ (30 mg) in Et₂O (60 mL) at 0 °C. The reaction mixture was allowed to warm to rt overnight, filtered and concentrated. Recrystallization from CH₂Cl₂/hexanes gave 1.42 g of compound 10A as a light yellow crystalline solid.

B. (3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-2-(3,5-Dichlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione (10B)

Compound 10A (1.42 g, 7.98 mmol, 1.0 eq) was combined with 3,5-dichloroaniline (1.55 g, 9.57 mmol, 1.2 eq) in AcOH (30 mL) and heated at 115 °C overnight. After the reaction mixture was cooled to room temperature, the resulting precipitate was collected, washed with MeOH and dried. Purification by flash chromatography on SiO₂ eluting with CH₂Cl₂ gave 1.63 g (63.5%) of compound 10B as a white crystalline solid. HPLC: 99% at 3.48 min (retention time) (YMC ODSA S5 C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% CF₃CO₂H, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 322.0 & 324.0 [M+H]⁺.

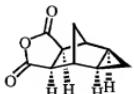
Example 11

(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione (11B)



5

A. (3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-4,6-methano-1H-cycloprop[f]isobenzofuran-1,3(3aH)-dione (11A)



- 10 Compound 11A was made in accordance with the procedure described in Kato, *et. al.*, *Chem. Lett.* 1823-1826 (1987), Kottwitz, *et. al.*, *Synthesis* 636-637 (1995). Creary, *et. al.*, *J. Org. Chem.* 40, 3326-3331 (1975) and Fieser & Fieser vol. 1, pg. 192. A mixture of 40% aq. KOH (11 mL) and Et₂O (40 mL) was cooled to 0 °C. *N*-Methyl-*N*'-nitro-*N*-nitrosoguanidine (3.6 g) was added portionwise to the mixture and stirred for 5 mins. The Et₂O layer was separated and added dropwise to a stirred solution of compound 4A (1 g, 6.09 mmol) and Pd(OAc)₂ (15 mg) in Et₂O (30 mL) and THF (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight, filtered and concentrated.
- 15 20 Recrystallization from CH₂Cl₂/hexanes gave 0.75 g of compound 11A as a white crystalline solid.

B. (3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione (11B)

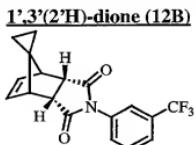
25

Compound **11A** (100 mg, 0.561 mmol, 1.2 eq) was combined with 1-amino-4-nitronaphthalene (88.0 mg, 0.468 mmol, 1.0 eq) in AcOH (2 mL) and heated at 115 °C overnight. After the reaction mixture was cooled to room temperature, the resulting precipitate was collected, washed with H₂O and dried to give 138.4 mg (85%) of compound **11B** as a dark brown crystalline solid. HPLC: 99% at 3.19 & 3.29 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 349.2 [M+H]⁺.

10

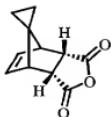
Example 12

(3a α ,4 α ,7 α ,7a α)-3a',4',7,7a'-Tetrahydro-2'-(3-(trifluoromethyl)phenyl)spiro[cyclopropane-1,8'-[4,7]methano[1H]isoindole]-1',3'(2'H)-dione (12B)



15

A. (3a α ,4 α ,7 α ,7a α)-3a',4',7,7a'-Tetrahydrospiro[cyclopropane-1,8'-[4,7]methanoisobenzofuran]-1',3'-dione (12A)



Compound **12A** was made in accordance with the procedure described in Alder, *et. al.*, *Chem. Ber.* **93**, 1888-1895 (1960). To a stirred solution of maleic anhydride (3.92 g, 39.9 mmol, 1 eq) in Et₂O (40 mL) at 0 °C was added spiro[2.4]hepta-4,6-diene (4 mL, 39.9 mmol, 1 eq) dropwise. After stirring for 1 day, the reaction mixture was concentrated and the resulting precipitate was filtered to give 2.5 g compound **12A** as a white powder.

5 B. (3a'α, 4'α, 7'α, 7a'α)-3a',4',7',7a'-Tetrahydro-2'-(3-(trifluoromethyl)phenyl)spiro[cyclopropane-1,8'-[4,7]methano[1H]isoindole]-1',3'(2'H)-dione (12B)

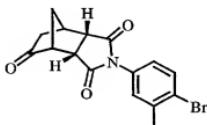
10 Compound 12A (100 mg, 0.526 mmol, 1.2 eq) was combined with 3-(trifluoromethyl)aniline (0.055 mL, 0.438 mmol, 1 eq) in acetic acid (2 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was isolated by filtration. The material was
15 washed sequentially with aqueous K₂CO₃ and water and then dried in a vacuum oven to provide 139.4 mg (95.5%) of compound 12B as a brownish-gray powder. HPLC: 95% at 3.29 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 334.0 [M+H]⁺.

15

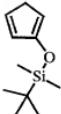
Example 13

(3aα,4aα,7aα,7aα)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-methano-1H-isoindole-1,3,5(2H,4H)-trione (13C)

20



A. (1,4-Cyclopentadien-1-ylxy)-(1,1-dimethylethyl)dimethylsilane (13A)

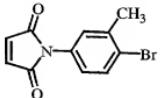


25 Cyclopentenone (2.5 mL, 29.8 mmol) was dissolved in methylene chloride (300 mL) followed by addition of TEA (6.23 mL, 44.7 mmol) and

cooling to 0°C. TMSOTf (5.40 mL) was then added dropwise over 5 minutes. The reaction was slowly warmed to 25°C and after 1.5 h, the reaction was filtered to remove the TEA salt. The solvent was removed *in vacuo* and compound **13A** was taken on crude.

5

B. 1-(4-Bromo-3-methylphenyl)-1H-pyrrole-2,5-dione (13B)



4-Bromo-3-methylaniline (1.55 g, 8.33 mmol) and maleic anhydride (0.898 g, 9.16 mmol) were dissolved in acetic acid (10 mL) and heated at 10 115 °C for 12 h. The reaction was then cooled to 25°C and the acetic acid was removed *in vacuo*. The resulting residue was suspended in 5% K₂CO₃ (100 mL), stirred for 25 minutes followed by filtering and rinsing with water. The material was then dried *in vacuo* to give compound **13B** as a light brown solid (1.65 g). HPLC: 100% at 2.96 min (retention time) (YMC 15 S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

C. (3α,4α,7α)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-methano-1H-isoindole-1,3,5(2H,4H)-trione (13C)

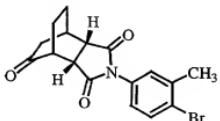
20

Compound **13A** (0.35 g, 2.26 mmol) was added to a suspension of compound **13B** (0.250 g, 0.94 mmol) in toluene (5.0 mL). The reaction was heated at 105°C for 5 h and then cooled to 25°C. The reaction was diluted with methylene chloride/TFA (20:1, 10 mL) and stirred for 1 h. The TFA was neutralized by addition of sat NaHCO₃. This was then extracted with methylene chloride (3 x 40 mL). The combined organics were dried over anhydrous Na₂SO₄. The crude material was purified by flash chromatography on SiO₂ eluting with 5% EtOAc/methylene chloride to give 0.173 g of compound **13C** as a white powder. HPLC: 100% at 3.093 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over

4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 365.0 [M+NH₄]⁺.

Example 14

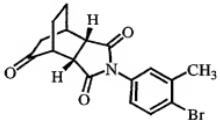
5 **(3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione (14)**



20 2-(trimethylsilyloxy)cyclohexadiene (Aldrich) (0.132 mL, 0.703 mmol) and compound 13B (0.075 g, 0.234 mmol) were heated in toluene (1.0 mL) at 110°C for 3 h. MeOH/HCl (4:1) 5 mL was then added and the reaction was stirred at rt for 1 h. The reaction was then diluted with methylene chloride and washed with sat NaHCO₃. The organics were then dried over anhydrous Na₂SO₄. The crude material was purified by preparative TLC eluting with 5% EtOAc in methylene chloride to give 15 0.057 g of compound 14 as a white solid. HPLC: 96% at 3.367 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 362.04 [M+H]⁺.

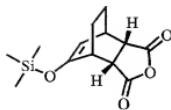
Example 15

(3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione (15B)



A. **(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-5-[(trimethylsilyl)oxy]-4,7-ethanoisobenzofuran-1,3-dione (15A)**

25



2-(trimethylsilyloxy)cyclohexadiene (Aldrich) (1.91 mL, 10.2 mmol) and maleic anhydride (1.00 g, 10.2 mmol) were heated in toluene (20 mL) at 110°C for

- 5 3 h. The reaction was then cooled to rt and the toluene removed in vacuo, to yield compound **15A** (2.5 g) as a yellow viscous oil of >90% purity by NMR. This material was taken on without further purification.

B. (3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-10 ethano-1H-isoindole-1,3,5(2H,4H)-trione (15B)

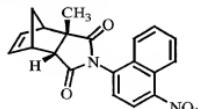
Compound **15A** (0.200 g, 0.752 mmol) and 3-methyl-4-bromoaniline (0.122 g, 0.752 mmol) were heated in AcOH (2.0 mL) for 14 h at 115°C. After cooling to rt, the reaction was poured into cold sat K_2CO_3 and stirred vigorously for

- 15 0.5 h. The mixture was then filtered and rinsed with water. The resulting tan solid was dried in vacuo giving 0.204 g of compound **15B**. HPLC: 96% at 3.367 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 362.04 [M+H]⁺.

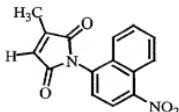
20

Example 16

(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-nitro-1-naphthalenyl)-3a-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (16B)



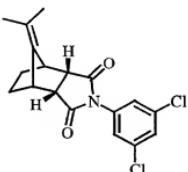
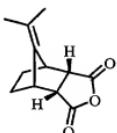
- 25 **A. 3-Methyl-1-(4-nitro-1-naphthalenyl)-1H-pyrrole-2,5-dione (16A)**



4-nitro-1-naphthalamine (2.00 g, 10.63 mmol) and citraconic anhydride (1.05 mL, 11.69 mmol) were dissolved in acetic acid (10 mL) and heated to 115 °C for 14 h. The reaction was then cooled to 25 °C and 5 transferred to cold sat K_2CO_3 with vigorous stirring. After 15 min, the solution was filtered, rinsed with water and dried under vacuum to yield 3.63 g of compound **16A** as a yellow solid. This material was taken on to the next step without further purification.

10 **B. (3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-nitro-1-naphthalenyl)-3a-methyl-4,7-methano-1H-isoindole-1,3(2H)-dione (16B)**

15 Compound **16A** (1.80 g, 6.38 mmol) and freshly cracked cyclopentadiene (1.68 g, 25.5 mmol) were dissolved in dichloroethane (10 mL) and stirred at 25 °C for 16 h. After 4 h, additional cyclopentadiene (1.68 mL, 25.5 mmol) was added. After 16 h, the volatiles were removed in vacuo and the resulting residue was purified by flash chromatography on SiO_2 eluting with 20% - 0% hexanes/methylene chloride. This yielded 2.01 g of compound **16B** as a pale yellow solid. HPLC: 100% at 3.093 20 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 366.2 [M+NH₄]⁺.

Example 17(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dichlorophenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione (17B)5 A. **(3 α ,4 α ,7 α ,7a α)-Hexahydro-8-(1-methylethylidene)-4,7-methanoisobenzofuran-1,3-dione (17A)**

Compound 17A was synthesized as described in L. R. Corwin; D. M. McDaniel; R. J. Bushby and J. A. Berson *J. Amer. Chem. Soc.* **102**, 10 276-287 (1980). Both the *endo* and *exo* isomers of the anhydride were isolated.

15 B. **(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dichlorophenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione (17B)**

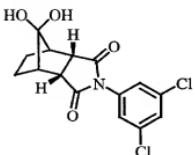
Compound 17A (endo isomer, 0.900 g, 4.37 mmol) and 3,5-dichloroaniline (0.644 g, 3.97 mmol) were dissolved in AcOH and then heated at 115°C for 14 h. The reaction was allowed to cool to 25°C and then the AcOH was removed in vacuo. The 20 resulting slurry was added to cold sat K₂CO₃ and stirred vigorously for 15 min. The suspension was then filtered and rinsed with water. The crude product was purified by flash chromatography on SiO₂ eluting with 20% hexanes/methylene chloride affording 1.14 g of compound 17B as a white solid. HPLC: 88% at 4.527 min

(retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 367.1 [M+H]⁺.

5

Example 18

(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dichlorophenyl)hexahydro-8,8-dihydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione (18)

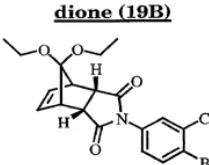


Compound **17B** (1.20 g, 3.43 mmol) was dissolved in CCl₄ (50 mL) and 10 methylene chloride (5 mL) and cooled to -25°C. O₃ was then bubbled through the reaction until a blue color persisted (~10 min). DMS (2.47 mL, 34.4 mmol) was then added and the reaction warmed to 25°C. After 12 h, a white precipitate formed and was filtered, rinsing with CCl₄ and dried to yield 1.01 g of compound **18** which was 95% pure by ¹H NMR spectroscopy and not stable to LC conditions employed. MS (ES): m/z 340.0 [M-H]⁻.

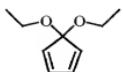
20

Example 19

(3 α ,4 α ,7 α ,7a α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-8,8-diehydroxy-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (19B)



A. 5,5-Diethoxy-1,3-cyclopentadiene (19A)



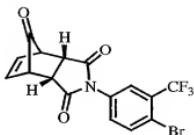
Compound **19A** was synthesized as described in P. E. Eaton, R. A. Hudson *J. Amer. Chem. Soc.* **87**, 2769-2770 (1965).

5 **B. (3 α ,4 α ,7 α ,7a α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-8,8-dioxy-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (19B)**

Freshly prepared compound **19A** (6.32 mmol) was added to 1-[4-bromo-3-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (0.400 g, 1.25 mmol, as prepared in Example **13B**) in Et₂O (50 mL) at 25°C. After 10 h, the reaction was concentrated *in vacuo* and purified by flash chromatography eluting with 20% - 10% hexanes/methylene chloride to give 0.501 g of compound **19B** as a white foam. HPLC: 100% at 4.203 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-15 90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 497.4 [M+Na]⁺.

Example 20

20 **(3 α ,4 α ,7 α ,7a α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3,8(2H)-trione (20)**



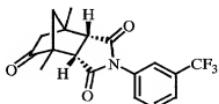
Compound **19B** (0.025 g, 0.052 mmol) in acetone (1.0 mL) and pTSA•H₂O (0.005 g) was added and the reaction was heated to reflux for 12 h. The volatiles were then removed *in vacuo* and the residue purified by preparative TLC eluting with 2.5% EtOAc/methylene chloride giving the compound **20** (0.021 g) as a pale yellow solid.

Not stable to LC conditions employed, purity (95%) determined by H^1 NMR spectroscopy. MS (DCI): m/z 399.7 [M+H] $^+$.

Example 21

5

(3ac,4 α ,7 α ,7a α)-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3,5(2H,4H)-trione (21C)

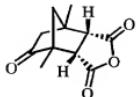


10 A. 3,5-Dimethyl-2-cyclopenten-1-one (21A)



Compound 21A was made in accordance with the procedure described in Toder, *et. al.*, *Synth. Commun.* 5, 435-439 (1975). To a stirred solution of diisopropylamine (17 mL, 121.2 mmol, 1 eq) in THF (300 mL) 15 at 0 °C under N₂ was added 2.5 M *n*-BuLi (53.3 mL, 133.3 mmol, 1.1 eq). The reaction mixture was cooled to -78 °C and HMPA (21 mL, 121.2 mmol, 1 eq) was added. After 30 min, 3-methyl-2-cyclopenten-1-one (12 mL, 121.2 mmol, 1 eq) was added, then 20 30 min later, methyl iodide (8.3 mL, 133.3 mmol, 1.1 eq) was added. The reaction mixture was stirred for a further 60 min at -78 °C, warmed to room temperature, quenched with sat. NH₄Cl, extracted with Et₂O (3X), dried over MgSO₄ and concentrated under reduced pressure. The crude product was distilled at atmospheric pressure and the fraction that came over between 165-178 °C was collected to give 10.5 g of compound 21A as 25 a light yellow oil.

B. (3 α ,4 α ,7 α ,7a α)-Tetrahydro-4,7-dimethyl-4,7-methanoisobenzofuran-1,3,5(4H)-trione

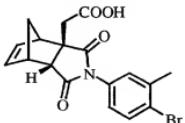


5

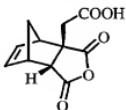
Compound **21A** (3.4 g, 30.87 mmol, 1 eq) and maleic anhydride (3.0 g, 30.87 mmol, 1 eq) were heated together at 100 °C in a sealed tube for 10 h. The resulting dark brown paste was triturated with hexanes containing a small portion of EtOAc. A portion of the paste dissolved and a precipitate eventually fell from the solution. The precipitate was isolated by filtration to give a light brown powder. Crude compound **21B** was taken on without further purification.

C. (3 α ,4 α ,7 α ,7a α)-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3,5(2H,4H)-trione (**21C**)

A solution of **21B** (154 mg, 0.74 mmol, 1.2 eq) and 3-(trifluoromethyl)aniline (0.077 mL, 0.616 mmol, 1 eq) in AcOH (3 mL) was heated 115 °C for 5 h. After cooling to rt, H₂O was added. The resulting precipitate was collected and washed with H₂O (1 X) with aq. NaHCO₃ (1 X) and with H₂O (3X) and dried to give 157.3 mg (73%) of **21C** as a tan powder. HPLC: 95% at 2.75 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm), MS (ES): m/z 352.0 [M+ H]⁺.

Example 22(3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)-1,2,3,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-3aH-isoindole-3a-acetic acid (22B)

- 5 A. (3 α ,4 α ,7 α ,7a α)-1,4,7,7a-Tetrahydro-1,3-dioxo-4,7-methanoisobenzofuran-3a(3H)-acetic acid (22A)



Cis-1,2,3-propenetricarboxylic acid anhydride (5.00 g, 32.1 mmol) was suspended in dichloroethane (30 mL) and freshly cracked

- 10 cyclopentadiene (4.23 g, 64.2 mmol) was added. The mixture was then heated at 80°C for 24 h, becoming homogenous after 3 h. Upon cooling to 25°C, the product precipitated out of solution and was filtered rinsing with 1:1 hexanes/methylene chloride. After drying *in vacuo*, 6.9 g of compound 22A was isolated as a white powder. NMR spectroscopy
15 showed only the endo isomer was isolated.

- B. (3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)-1,2,3,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-3aH-isoindole-3a-acetic acid (22B)

- 20 Compound 22A (1.00 g, 4.50 mmol) and 4-bromo-3-methylaniline (0.754 g, 4.05 mmol) were dissolved in AcOH (10 mL) and heated to 112°C for 14 h. After cooling to 25°C, the AcOH was removed *in vacuo* and the resulting residue transferred to cold sat K₂CO₃. The resulting precipitate was isolated by filtration and rinsed with water. The crude solid was purified by preparative reverse phase HPLC
25

(10 – 90% aqueous methanol) to give 0.787 g of compound **22B** as a white foam. HPLC: 100% at 2.943 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 391.17 [M+H]⁺.

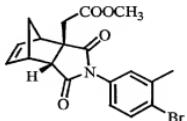
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Example 23

(3ac,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)-1,2,3,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-3aH-isoindole-3a-acetic acid, methyl ester

(23)

10



Compound **22B** (0.020 g, 0.051 mmol) was dissolved in MeOH (2.0 mL) and H₂SO₄ (1 drop) was added. The mixture was then heated at 64°C for 2 h. After cooling to 25°C, the reaction was poured into sat NaHCO₃. This mixture was

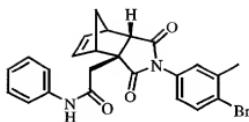
15 extracted with methylene chloride (3 x 10 mL) and the combined organics were dried over anhydrous Na₂SO₄. Removal of the volatiles gave 0.018 g of compound **23** as a white solid. No purification was necessary. HPLC: 95% at 3.187 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 405.3 [M+H]⁺.

20

Example 24

(3ac,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)-1,2,3,4,7,7a-hexahydro-1,3-dioxo-N-phenyl-4,7-methano-3aH-isoindole-3a-acetamide (24)

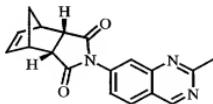
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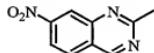
Compound **22B** (0.100 g, 0.256 mmol) was dissolved in methylene chloride (1.5 mL). TEA (0.060 mL, 0.435 mmol) and then 2,6-benzoyl chloride (0.037 mL, 0.256 mmol) were added. The reaction was then stirred at 25°C for 16 h. 5 Benzylamine (0.023 mL, 0.256 mmol) was then added followed by 4-DMAP (cat). After 3 h, the volatiles were removed *in vacuo* and the resulting residue was purified by preparative reverse phase HPLC (YMC S5 ODS 30 x 250 mm column, 25 mL/min, 0-100% in 30 mins) to give 0.010 g of compound **24** as a white solid. HPLC: 100% at 10 3.597 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 464.15 [M+H]⁺.

Example 25

15 **(3a α ,4 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-methyl-7-quinazolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (25D)**



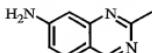
A. 2-Methyl-7-nitroquinazoline (25A)



20 2-Fluoro-4-nitrobenzaldehyde (1.00 g, 5.92 mmol) and acetamidine hydrochloride (0.783 g, 8.28 mmol) were added to a suspension of activated 4Å MS (1.2 g) in acetonitrile (60 mL). K₂CO₃ (1.14 g, 8.28 mmol) was then added and the reaction was heated to reflux for 4 h. The reaction was then cooled to 25°C and filtered through celite rinsing with 25 CH₂Cl₂. The crude product was purified by flash chromatography on silica

eluting with 0 – 10% acetone in CH_2Cl_2 to give 0.386 g of compound **25A** as a yellow solid.

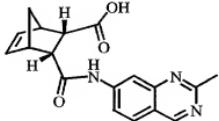
B. 7-Amino-2-methylquinazoline (25B)



Compound **25A** (0.400 g, 2.12 mmol) was dissolved in EtOAc (20 mL) and Pd/C (10% Pd, 0.045 g) was added. Hydrogen was then introduced to the flask with a balloon. After 6 h, the reaction was filtered through celite rinsing with EtOAc. Concentration *in vacuo* gave compound **25B** as a yellow solid (0.311 g). This was taken on without purification to subsequent reactions.

10

C. (*endo, endo*)-3-[[2-Methyl-7-quinazolinyl]amino]carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (25C)



Compound **25B** (0.100 g, 0.629 mmol) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (0.132 g, 0.818 mmol) were suspended in THF (3.0 mL) and heated to reflux for 3 h. The mixture became homogenous upon initial heating and then a yellow precipitate formed as the reaction progressed. After cooling to 25°C, the mixture was filtered and rinsed with THF to yield 0.088 g of compound **25C**. This material was carried to the next step without further purification.

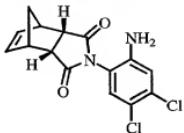
D. **(3 α ,4 α ,7 α ,7 α)-3a,4,7,7a-Tetrahydro-2-(2-methyl-7-quinazolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (25D)**

Compound **25C** (0.051 g) was suspended in Ac₂O (1.0 mL) and heated to 140°C for 1.5 h. After cooling to 25°C, the solution was poured into cold sat K₂CO₃ and stirred to 0.5 h. The solution was then filtered, rinsed with water and the isolated solid was dried under vacuum to yield 0.029 g of compound **25D** as yellow powder. The compound was not stable to LC conditions employed, purity (95%) was determined by H¹ NMR spectroscopy. MS (ES): m/z 306.2 [M+H]⁺.

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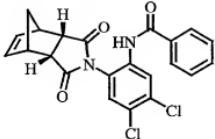
Example 26

(3 α ,4 α ,7 α ,7 α)-2-(2-Amino-4,5-dichlorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (26)



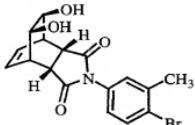
15 1,2-Diamino-4,5-dichlorobenzene (1.00 g, 5.65 mmol) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (1.02 g, 6.21 mmol) were dissolved in THF (5.0 mL) and heated to 85°C in a sealed tube for 3 h. After cooling to 25°C the volatiles were removed in vacuo and the resulting brown residue was diluted with absolute ethanol and cooled to -20°C. After 2 h, the product crashed out and was 20 filtered rinsing with cold ethanol. The brown colored solid was recrystallized from absolute ethanol to give 1.39 g of compound **26** as a white solid. HPLC: 99% at 4.190 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 324.10 [M+H]⁺.

25

Example 27**(3a α ,4 α ,7 α ,7a α)-N-[4,5-Dichloro-2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)phenyl]benzamide (27)**

- 5 Compound **26** (0.050 g, 0.155 mmol) was dissolved in methylene chloride (3.0 mL) and pyridine (0.038 mL, 0.465 mmol) and 4-DMAP (~5 mg) were added. The mixture was cooled to 0°C and benzoyl chloride (0.022 mL, 0.186 mmol) was added. The reaction was warmed to 25°C and after 2 h, the volatiles were removed *in vacuo*. The resulting residue was purified by preparative TLC eluting with 7%
 10 EtOAc/methylene chloride to afford 0.066 g of compound **27** as a white solid. HPLC: 100% at 3.850 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 428.08 [M+H]⁺.

15

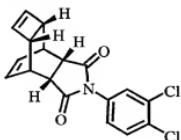
Example 28**(3a α ,4 β ,5 α ,6 α ,7 β ,7a α)-2-(4-Bromo-3-methylphenyl)hexahydro-5,6-dihydroxy-4,7-etheno-1H-isoindole-1,3(2H)-dione (28)**

- Compound **13B** (0.045 g, 0.17 mmol) and cis-1,2-dihydrocatechol (0.057 g, 20 0.51 mmol) were dissolved in toluene (1.0 mL) and heated to 100°C for 3 days. The crude reaction mixture was purified by preparative silica gel TLC to yield 41 mg (66% yield) of compound **28** as a white solid. Compound **28** was crystallized from 1:1 acetone/hexane to yield crystals adequate for structural determination. HPLC: 66% at 2.77 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90%

aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm, MS (ES): m/z 378.01 [M]⁺.

Example 29

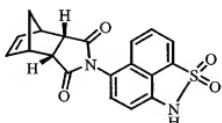
- 5 (3 α ,4 β ,4 α ,6 α ,7 β ,7 α)-2-(3,4-Dichlorophenyl)-3 α ,4,4 α ,6 α ,7,7a-hexahydro-4,7-etheno-1H-cyclobut[f]isoindole-1,3(2H)-dione (29)



- 3,5-Dichloroaniline (0.027 g, 0.165 mmol) and 10-oxatetacyclo-(6.3.0.2,7.0.3,6)trideca-4,12-diene-9,11-dione (0.040 g, 0.197 mmol, Aldrich 10 Chemicals) was dissolved in acetic acid (1.0 mL) and was heated to 112°C for 12 hours. The solution was allowed to cool to room temperature for 4.5 hours and the resulting precipitate was isolated by filtration, washed with acetic acid followed by hexane and then dried under vacuum to yield 54 mg of compound 29 as a white solid. Compound 29 was crystallized from 1:1 methylene chloride/methanol to yield crystals 15 adequate for structural determination. HPLC: 66% at 2.77 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 346.04 [M+H]⁺.

20 **Example 30**

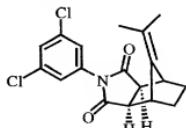
- (3 α ,4 α ,7 α ,7a α)-2-(1,1-Dioxido-2H-naphth[1,8-cd]isothiazol-5-yl)-3 α ,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (30)



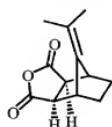
5 *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (26 mg, 0.16 mmol, 1.2 eq) was combined with 5-amino-1,8-naphthosultam (25 mg, 0.13 mmol, 1.0 eq, synthesized as described in EP-350403 and Hammouda, *et al.*, *J. Heterocycl. Chem.* **21**, 337-339 (1984)) in acetic acid (0.6 mL) and
10 heated at 115 °C overnight. The solvent was removed under reduced pressure and the residue was purified by Prep HPLC to give 21% yield of compound **30** as a brown solid. HPLC: 97% at 2.18 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 365.1 [M+H]⁺

Example 31

(3 α ,4 β ,7 β ,7 α)-2-(3,5-Dichlorophenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione (31B)



15 A. **(3 α ,4 β ,7 β ,7 α)-Hexahydro-8-(1-methylethylidene)-4,7-methanoisobenzofuran-1,3-dione (31A)**



20 Compound **31A** was synthesized as described in L. R. Corwin; D. M. McDaniel; R. J. Bushby and J. A. Berson *J. Amer. Chem. Soc.* **102**, 276-287 (1980). Both the *endo* and *exo* isomers of the anhydride were isolated.

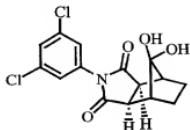
B. (3 α ,4 β ,7 β ,7 α)-2-(3,5-Dichlorophenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione (31B)

5 Compound **31A** (exo isomer, 0.386 g, 1.87 mmol) and 3,5-dichloroaniline (0.276 g, 1.70 mmol) were dissolved in AcOH (4.0 mL) and then heated at 115°C for 14 h. The reaction was allowed to cool to 25°C and then the AcOH was removed in vacuo. The resulting slurry was added to cold sat K_2CO_3 and stirred vigorously for 15 min. The suspension was then filtered and rinsed with water. The crude product was 10 purified by flash chromatography on SiO_2 eluting with 20% hexanes/methylene chloride affording 0.598 g of compound **31B** as a white solid. HPLC: 100% at 3.950 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 367.1 [M+H]⁺.

15

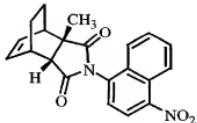
Example 32

(3 α ,4 β ,7 β ,7 α)-2-(3,5-Dichlorophenyl)hexahydro-8,8-dihydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione (32)

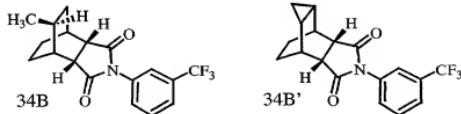


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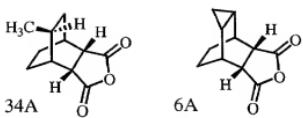
Compound **31B** (0.250 g, 0.72 mmol) was dissolved in CCl_4 (10 mL) and methylene chloride (1 mL) and cooled to -25°C. O_3 was then bubbled through the reaction until a blue color persisted (~10 min). DMS (0.53 mL, 7.20 mmol) was then added and the reaction warmed to 25°C. After 12 h, a white precipitate formed and 25 was filtered, rinsing with CCl_4 and dried to yield 0.193 g of compound **32** (95% pure by H^1 NMR spectroscopy, not stable to LC conditions). MS (ES): m/z 340.0 [M-H]⁻. The *exo* diastereomer was confirmed by determination of the X-ray crystal structure.

Example 33**(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-3a-methyl-2-(4-nitro-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione (33)**

- 5 Compound **16A** (0.250 g, 0.88 mmol) and 1,3-cyclohexadiene (0.142 g, 1.77 mmol) were dissolved in toluene (2.0 mL). The mixture was then heated to 125°C in a sealed tube for 20 h. The solution was then cooled to 25°C and the toluene removed *in vacuo*. The resulting residue was purified by flash chromatography on SiO₂ eluting with 30% - 10% - 0% hexane in CH₂Cl₂ to give
- 10 0.121 g of compound **33** as a yellow solid. HPLC: 100% at 2.99 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 363.0 [M+H]⁺.

Example 34**(3a α ,4 β ,5 β ,7 β ,7a α)-Hexahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3(2H)-dione (34B) & (3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione (34B')****20 1,3(2H,3aH)-dione (34B')**

- A. **(3a α ,4 β ,5 β ,7 β ,7a α)-Hexahydro-5-methyl-4,7-ethanoisobenzofuran-1,3-dione (34A) & (3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-Hexahydro-4,6-etheno-1H-cycloprop[f]isobenzofuran-1,3(3aH)-dione (6A)**
- 25



To a solution of compound **5A** (33.5 g, 176 mol) in 200 ml of acetone was added Pd/C (10% Pd, 2.00 g). The mixture was put under a hydrogen balloon for 4 h with stirring. The solution was filtered through celite, evaporated under vacuum and then taken up in 250 ml of ethyl acetate. To this solution was added Pd/C (10% Pd, 1.87 g) and the mixture was stirred under a hydrogen balloon for 21 h. The solution was filtered through celite and the filtrate was evaporated under vacuum. The resulting white solid was recrystallized twice with a 50/50 mixture of CH_2Cl_2 / hexane and followed by a recrystallization with 100% ethyl acetate to yield 3.2 g of a final white solid which was a 1:10 mixture of compounds **34A** & **6A**.

15 B. (3 α ,4 β ,5 β ,7 β ,7 α)-Hexahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3(2H)-dione (34B) & (3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione (34B')

20 A solution of compounds **34A** & **6A** (1:10, 2.3 g, 12.09 mmol, 1.2 eq) and 3-(trifluoromethyl)aniline (1.26 mL, 10.08 mmol, 1 eq) in AcOH (60 mL) was heated at 115 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized 25 from CH₂Cl₂/hexanes to give 2.67 g (79%) of compounds **34B** & **34B'** in a 1:10 ratio by ¹H NMR. Separation by preparative HPLC 45 min (YMC S10 ODS SH-365-10, 10-90% aqueous CH₃CN over 75 minutes, 4 mL/min, monitoring at 220 nm) gave 211 mg of compound **34B** as an off-white

crystalline solid and 2.07 g of compound **34B'** as a white crystalline solid.

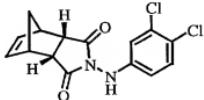
Compound **34B'**: HPLC: 99% at 3.63 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z

- 5 338.1 [M+H]⁺. Compound **34B'**: HPLC 99% at 3.47 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 336.2[M+H]⁺.

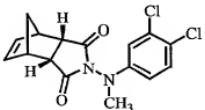
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Example 35

(3a α ,4 α ,7 α ,7a α)-2-[(3,4-Dichlorophenyl)amino]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (35)

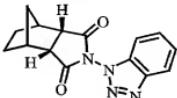


- 3,4-Dichlorophenylhydrazine hydrochloride (213.5 mg, 1.0 mmol) and *cis*-15 5-norbornene-endo-2,3-dicarboxylic anhydride (164.2 mg, 1.0 mmol) were combined in ethanol (20 mL). To this solution was added 324 mg (1.0 mmol) of sodium ethoxide (21 wt. % solution in denatured ethyl alcohol). The reaction mixture was refluxed for 5 h. The reaction was allowed to cool to rt, and the resulting precipitate was collected by filtration, washed with water and ethanol and dried *in vacuo* to give 20 236 mg of compound **35** (73%) as an off-white solid. HPLC: 98% at 3.090 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm), MS (ESI): m/z 321.0 & 323.0 [M-H]⁻.

Example 36**(3 α ,4 α ,7 α ,7 α)-2-[(3,4-Dichlorophenyl)methylamino]-3 α ,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (36)**

5

To a solution of compound **35** (130 mg, 0.40 mmol) in 10 ml of THF was added sodium hydride (32 mg, 0.80 mmol, 60% dispersion in mineral oil), followed by iodomethane (114 mg, 0.80 mmol). The reaction mixture was stirred at rt for 2 h, and quenched by addition of sat NH_4Cl . The reaction mixture was extracted with dichloromethane (3x50 ml) and the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. Flash chromatography (silica, dichloromethane) provided compound **36**, (67 mg, 50%), as a white solid. HPLC: 100% at 3.323 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 391.12 [M+MeOH+Na]⁺.

Example 37**(3 α ,4 α ,7 α ,7 α)-2-(1H-Benzotriazol-1-yl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (37)**

20

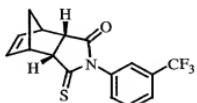
Compound **50A** (116.8 mg, 0.703 mmol, 1.0 eq) was combined with 1-aminobenzotriazole (94.3 mg, 0.703 mmol, 1.0 eq) in AcOH (2 mL) and heated at 115 °C overnight. After the reaction mixture was cooled to room temperature, the reaction solution was concentrated under reduced pressure and the resulting solid was washed with MeOH and dried over MgSO_4 to give 124 mg (61%) of compound **37** as a brown solid. HPLC 99%

at 2.47 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 283.21 [M+H]⁺

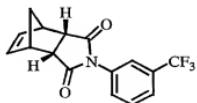
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Example 38

(3 α ,4 α ,7 α ,7a α)-2,3,3a,4,7,7a-Hexahydro-3-thioxo-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindol-1-one (38B)



- 10 A. (3 α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione (38A)



- 15 *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (2.0 g, 12.2 mmol, 1.2 eq) was combined with 3-(trifluoromethyl)aniline (1.3 mL, 10.2 mmol, 1 eq) in acetic acid (80 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was isolated by filtration. The material was washed sequentially with aqueous K₂CO₃ and water and then dried.
- 20 Recrystallization from CH₂Cl₂/hexanes gave 2.01 g (63%) of compound 38A as a white crystalline solid. HPLC: 99% at 1.67 min (Phenom-Prime S5 C18 column 4.6 x 30 mm, 10-90% aqueous methanol over 2 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 340.15 [M+MeOH]⁺

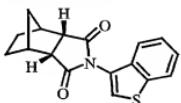
25

B. (3 α ,4 α ,7 α ,7 α)-2,3,3a,4,7,7a-Hexahydro-3-thioxo-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindol-1-one (38B)

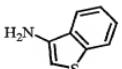
5 A solution of compound 38A (191 mg, 0.622 mmol, 1 eq) and Lawesson's Reagent (126 mg, 0.311 mmol, 0.5 eq) in toluene was heated to reflux for 12 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography eluting with CHCl₃ to give compound 38B (31.6 mg, 16%) as a yellow solid. HPLC: 95% at 3.50 min
10 (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 323.8 [M+H]⁺

Example 39

15 (3 α ,4 α ,7 α ,7 α)-2-(Benzo[b]thiophen-3-yl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (39B)



A. 3-Aminobenzo[b]thiophene (39A)



20 A solution of methyl-3-aminobenzothiophene-2-carboxylate (1 g, 4.83 mmol, 1 eq) in 1-methyl-2-pyrrolidinone (8 mL) and piperazine (2.08 g, 24.13 mmol, 5 eq) was stirred at 130 °C overnight. Ice was added, and the mixture was extracted with EtOAc. The organic extracts were washed twice with water, dried, and concentrated *in vacuo*. The crude material
25 was purified by flash chromatography on silica gel eluting with 33% ethyl acetate in hexanes to provide 600 mg (83%) of compound 39A as a yellow oil. HPLC: 98% at 1.043 min (retention time) (YMC S5 ODS 4.6 x 50 mm,

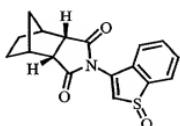
10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm).

5 **B. (3a α ,4 α ,7 α ,7a α)-2-(Benzo[b]thiophen-3-yl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (39B)**

10 Compound **50A** (200 mg, 1.2 mmol, 1.0 eq) was combined with compound **39A** (197 mg, 1.33 mmol, 1.1 eq) in acetic acid (4 mL) and heated at 110 °C overnight. After the reaction was allowed to cool to rt, 10 water was added, and the resulting precipitate was isolated by filtration. The material was washed with methanol and then dried under vacuum to provide 160 mg (44.9%) of compound **39B** as a brown solid. HPLC: 98% at 2.92 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm), MS (ES): m/z 298.32 [M+ H]⁺.

15 **Example 40**

20 **(3a α ,4 α ,7 α ,7a α)-Hexahydro-2-(1-oxidobenzo[b]thiophen-3-yl)-4,7-methano-1H-isoindole-1,3(2H)-dione (40)**



25 A solution of compound **39B** (20 mg, 0.067 mmol, 1 eq) and TFA (0.12 ml) in CH₂Cl₂ was stirred for 5 minutes. A 30% aqueous solution of H₂O₂ (0.008 ml, 0.067 mmol, 1 eq) was added and the resulting mixture was stirred at room temperature and monitored by HPLC. After 4 hours, a solution of saturated aqueous NaHCO₃ was added and the resulting mixture was extracted with CH₂Cl₂. The organic layer was concentrated

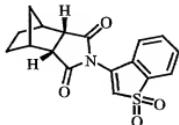
under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 10% EtOAc/CH₂Cl₂, to give 15 mg (71%) of compound **40** as a light yellow solid. HPLC: 99% at 2.24 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm), MS (ES): m/z 346.15 [M+ H]⁺.

Example 41

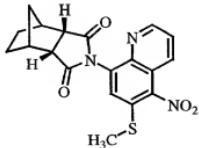
(3 α ,4 α ,7 α ,7 α)-2-(1,1-Dioxidobenzo[b]thiophen-3-yl)hexahydro-4,7-

10

methano-1H-isoindole-1,3(2H)-dione (41)



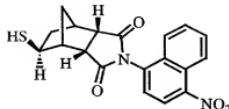
*m*CPBA (60% mixture, 48.8 mg, 0.283 mmol, 2.4 eq) was added to a solution of compound **39B** (35 mg, 0.118 mmol, 1 eq) in CH₂Cl₂ (3 mL) and the mixture was stirred at room temperature overnight. Additional *m*CPBA (20 mg, 0.116 mmol, 1 eq) was added and the mixture was stirred for 4 more hours to drive the reaction to completion. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 4% EtOAc/CH₂Cl₂. The resulting solid was washed with methanol to remove a small amount of impurity and dried under vacuum to give 25 mg (64.4%) of compound **41** as a light yellow solid. HPLC: 99% at 2.39 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm), MS (ES): m/z 347.0 [M+ NH₄]⁺.

Example 42(3a α ,4 α ,7 α ,7a α)-Hexahydro-2-[6-(methylthio)-5-nitro-8-quinolinyl]-4,7-methano-1H-isoindole-1,3(2H)-dione (42)

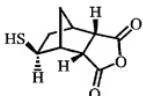
5 Compound **50A** (100 mg, 0.602 mmol, 1.0 eq) was combined with 8-amino-6-(methylthio)-5-nitroquinoline (141 mg, 0.602 mmol, 1.0 eq) in acetic acid (3 mL) and heated at 115 °C overnight. The reaction mixture was added to aqueous NaHCO₃ and extracted with CH₂Cl₂ (3X). The combined organic layers were washed with H₂O (1X), dried over MgSO₄

10 and concentrated under reduced pressure. The resulting solid was recrystallized from CH₂Cl₂/hexanes to give compound **42** as a yellow crystalline solid in 56.5% yield. HPLC: 97% at 3.05 & 3.18 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 384.30 [M+H]⁺

15

Example 43(3a α ,4 α ,5 α ,7 α ,7a α)-Hexahydro-5-mercaptop-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (43B)

A. (3a α ,4 α ,5 α ,7 α ,7a α)-Hexahydro-5-mercaptop-4,7-methanoisobenzofuran-1,3-dione (43A)



Compound **43A** was made in accordance with the procedure

5 described in Haché, *et. al.*, *Tetrahedron Lett.* **35**, 1837-1840 (1994). A solution of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (1 g, 6.09 mmol, 1 eq), triphenylsilanethiol (2 g, 6.94 mmol, 1.14 eq) and AIBN (1 g, 6.09 mmol, 1 eq) in benzene (6 mL) was heated to reflux for 15 h. After cooling to rt, TFA (2.35 mL, 30.46 mmol, 5 eq) was added and the mixture 10 was stirred for 30 min. Concentration under reduced pressure and purification by flash chromatography eluting with 25% EtOAc/hexanes gave 300 mg of impure compound **43A** which was used directly in the next step.

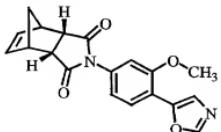
15 **B.** (*3a*o,4o,5o,7o,7ac)-Hexahydro-5-mercaptop-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione (**43B**)

Compound **43A** (76 mg, 0.383 mmol, 1.0 eq) was combined with 4-nitro-1-naphthalamine (54 mg, 0.289 mmol, 0.75 eq) in acetic acid (2 mL) and heated at 115 °C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was isolated by filtration. The material was washed sequentially with aqueous K_2CO_3 and water and then dried to give material that was 72% pure. Purification by prep HPLC: 10.10 min (YMC ODS 20 X 100 mm, 10-90% aqueous methanol over 20 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 14.2 mg (10%) of compound **43B** (forms disulfide over time). HPLC: 80% (+12% disulfide) at 3.02 & 3.15 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing

0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 300.31 [M+H]⁺

Example 44

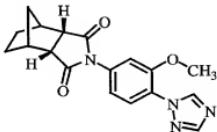
5 **(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-[3-methoxy-4-(5-oxazolyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione (44)**



3-Methoxy-4-(oxazol-5-yl)phenylamine (51 mg, 0.27 mmol, prepared as described in WO 00/25780) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride 10 (44 mg, 0.27 mmol) were combined in acetic acid (2 mL) and heated at 110 °C for 1 hr. After the reaction was allowed to cool to rt, the acetic acid was removed under reduced pressure. The residue was washed with methanol to give 90 mg (72%) of compound 44 as a light brown solid. HPLC: 98% at 2.583 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes 15 containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 337.31 [M+H]⁺.

Example 45

20 **(3a α ,4 α ,7 α ,7a α)-Hexahydro-2-[3-methoxy-4-(1H-1,2,4-triazol-1-yl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione (45)**



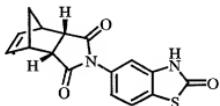
Compound 50A (26 mg, 0.16 mmol, 1.2 eq) was combined with 3-methoxy-4-(1H-1,2,4-triazol-1-yl)-benzenamine (25 mg, 0.13 mmol, 1.0 eq, synthesized as described in WO-0025780) in acetic acid (0.6 mL) and

heated at 115 °C overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with 70% EtOAc/CH₂Cl₂, to give 30.9 mg (70%) of compound **45** as a white solid. HPLC: 99% at 2.41 min (retention time) (YMC S5 ODS 5 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% H₃PO₄, monitoring at 220 nm), MS (ES): m/z 339.17 [M+ H]⁺.

Example 46

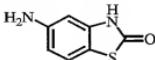
(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-2-oxo-6-benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (46B)

10



A. 6-Amino-2-benzothiazolinone (46A)

15



20

A solution of 6-nitro-2-benzothiazolinone (98 mg, 0.50 mmol) in 20 mL of EtOAc with 10% Pd/C (~20 mg) was stirred under H₂ balloon for 4 h. The reaction mixture was filtered through celite eluting with EtOAc, concentrated under reduced pressure to give 80 mg of 6-amino-2-benzothiazolinone.

B. (3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-2-oxo-6-benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (46B)

25

Compound **46A** (80 mg, 0.48 mmol) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (82 mg, 0.50 mmol) were combined in acetic acid (2 mL) and heated at 110 °C for 5 h. After the reaction was allowed to cool to rt, the acetic acid was removed under vacuum. The residue was washed with methanol to give 96 mg

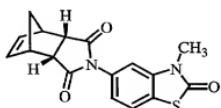
(64%) of compound **46B** as a white solid. HPLC: 100% at 2.133 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 313.04 [M+H]⁺.

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Example 47

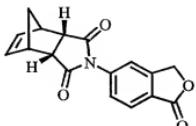
(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-3-methyl-2-oxo-6-benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (47)

10

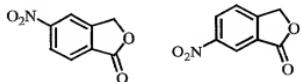


To a solution of compound **46B** (50 mg, 0.16 mmol) in 5 ml of DMF was added potassium carbonate (221 mg, 1.6 mmol) and iodomethane (45 mg, 0.32 mmol). The mixture was stirred at rt for 4 hr and then quenched by adding water.

- 15 The reaction mixture was extracted with dichloromethane (3 x 25 ml). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. Flash chromatography (silica, 1% methanol/dichloromethane) provided compound **47** as a white solid (45 mg, 87%). HPLC: 100% at 2.613 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 327.04 [M+H]⁺.
- 20

Example 48**(3a α ,4 α ,7 α ,7a α)-2-(1,3-Dihydro-3-oxo-6-isobenzofuranyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (48C)**

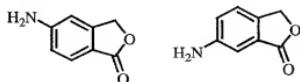
5

A. 5-nitro & 6-nitrophthalides (48A)

Compound **48A** (5-nitro- and 6-nitrophthalides) were made in accordance with the procedure described in Watanabe *et. al.*, *Chem. Pharm Bull.* **26** (2), 530-538

- 10 (1978). To a suspension of 4-nitrophthalimide (3 g, 15.6 mmol) in 60 ml of 90% methanol was added NaBH₄ (900 mg, 23.8 mmol). The mixture was stirred at rt for 2 h and then quenched by addition of 30 ml of 10% HCl. The aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. Flash chromatography (silica, dichloromethane) provided compound **48A** as a white solid (840 mg, 30%) with a ratio 1:2, favoring the 6-nitrophthalide isomer. HPLC: 100% at 1.507 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm).
- 15

20

B. 5-Amino, 6-aminophthalides (48B)

Compound **48A** (5-nitro- and 6-nitrophthalides, 810 mg, 4.50 mmol) was taken up in a mixture of 10 ml of acetic acid and 10 ml of ethyl acetate. To this

mixture was added 10% Pd/C (162 mg, 20% by weight) and the reaction was stirred under H₂ (balloon) for 16 hr. The reaction mixture was filtered through celite eluting with EtOAc and concentrated under reduced pressure to give compound **48B** (5-amino- and 6-aminophthalides, 1:2 ratio). The crude mixture was taken on without further purification.

C. (3a α ,4 α ,7 α ,7a α)-2-(1,3-Dihydro-3-oxo-6-isobenzofuranyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (48C)

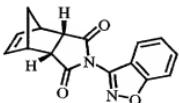
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Compound **48B** (crude mixture, 1:2 ratio of 5-amino- and 6-aminophthalide) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (886 mg, 5.4 mmol) were combined in acetic acid (10 mL) and heated at 110 °C for 5 h. After the reaction was allowed to cool to rt, the acetic acid was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, dichloromethane) and preparative HPLC to give compound **48C** (118 mg) as a white solid. HPLC: 98% at 2.213 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 296.01 [M+H]⁺.

20

Example 49

(3a α ,4 α ,7 α ,7a α)-2-(1,2-Benzisoxazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (49)



25

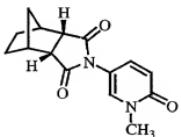
3-Amino-1,2-benzisoxazole (47 mg, 0.54 mmol, prepared as described in Shutske *et. al.*, *J. Heterocycl. Chem.* **26**, 1293-1298 (1989)) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (69 mg mg, 0.42 mmol) were combined in acetic acid (1 mL) and heated at 110 °C for 20 h. After the reaction was allowed to cool to

rt, the acetic acid was removed under reduced pressure. To the resulting gum was added 5 ml of saturated NaHCO₃ and 10 ml of CH₂Cl₂ and the mixture was stirred at rt for 30 minutes. The organic layer was isolated, dried over MgSO₄ and dried under vacuum. The residue was purified by flash chromatography (silica, 0.5 % MeOH in CH₂Cl₂) to give compound **49** (50 mg, 51%) as a white solid. HPLC: 98% at 2.54 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid., 4 mL/min, monitoring at 220 nm), MS (ES): m/z 303.08 [M+Na]⁺.

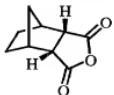
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Example 50

(3 α ,4 α ,7 α ,7a α)-2-(1,6-Dihydro-1-methyl-6-oxo-3-pyridinyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (50D)

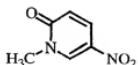


15

A. *cis*-Norbornane-*endo*-2,3-dicarboxylic anhydride (50A)

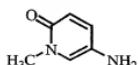
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A solution of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (5 g, 31.4 mmol) and 10% Pd/C (~100 mg) in a mixture of EtOAc and EtOH was shaken under H₂ at 55 psi for 3 h. The reaction solution was filtered through a pad of celite eluting with EtOAc and concentrated to give 10 g of compound **50A** as a white powder.

B. 1-Methyl-5-nitro-2(1H)-pyridinone (50B)

To a solution of 2-hydroxy-5-nitropyridine (600 mg, 4.28 mmol, 1 eq)

- 5 in DMF (5 mL) was added cesium carbonate (1.67 g, 5.16 mmol, 1.2 eq), followed by methyl iodide (0.4 mL, 6.42 mmol, 1.5 eq). After stirring overnight, the reaction mixture was quenched with water and extracted with ethyl ether (5 X 20 mL). The ether was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was column chromatographed, eluting with 50% EtOAc/hexanes to give 450 mg of compound **50B**.

C. 5-Amino-1-methyl-2(1H)-pyridinone (50C)

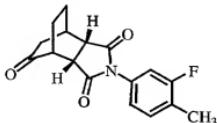
- 15 A solution of compound **50B** (200 mg, 1.298 mmol) and 10% Pd/C (~5 mg) in MeOH and AcOH was stirred under H_2 at 1 atmosphere for 30 minutes. The reaction solution was filtered through a pad of celite eluting with MeOH. The MeOH was removed under reduced pressure to give compound **50C**.

- 20 **D. (3a α ,4 α ,7a α)-2-(1,6-Dihydro-1-methyl-6-oxo-3-pyridinyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (50D)**

- Compound **50C** in AcOH was combined with compound **50A** (209 mg, 25 1.298 mmol, 1 eq) in acetic acid (4 mL) and heated at 165°C for 6 h. The acetic acid was distilled off and the material was washed with aqueous K_2CO_3 and water. The crude material was column chromatographed, eluting with 50% EtOAc/ hexanes to give 260 mg of compound **50D** as a white solid. HPLC: 99 % at 1.62 min (retention

time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 273.0 [M+H]⁺.

5

Example 51**(3 α ,4 α ,7 α ,7 α)-2-(3-Fluoro-4-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione (51)**

10 The below procedure describes a general approach for the production of solution phase combinatorial libraries of compounds of formula **I**. The general procedure described can be extrapolated from the processes described above in Step B of Example 1 (“**1B**”), Step B of Example 2 (“**2B**”), and Step C of Example 7 (“**7C**”) where anhydride-like 15 intermediates such as compounds **6A** or **15A** or commercially available anhydrides such as **1,2-cyclohexanedicarboxylic anhydride**, **endo-bicyclo(2.2.2)-5-octene-2,3-dicarbo anhydride** or **cis-5-norbornene-endo-2,3-dicarboxylic anhydride** can replace the intermediate compounds **1A**, **2A**, or **7B**. Other anhydride-like intermediates which can be used in 20 replacement of compounds **1A**, **2A**, or **7B** are, but are not limited to, compounds **3A**, **4A**, **5A**, **8B**, **9A**, **10A**, **11A**, **12A**, **15A**, **17A**, **22A**, **31A**, **34A**, and **50A**.

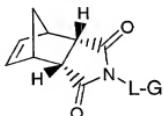
25 The specific procedure shown describes in detail the synthesis of a library of compounds derived from the reaction of the intermediate compound **15A** with an array of substituted aniline intermediates. In this Example, specific data is given on one example compound from this library; data on other compounds so obtained is provided in the following Tables. This general procedure can be modified by one skilled in the art to

accommodate the synthesis of an array of compounds derived from related anhydide and aniline intermediates.

- 4-Methyl-3-fluoroaniline (0.010 g, 0.08 mmols) was dissolved in acetic acid (0.400 mL) and transferred to a 1.5 mL conical vial with a 5 septa cap. Stock solutions of an additional 95 amines were prepared as described above. To each of the above vials was added 0.4 mL (0.12 mmol) of a stock solution of compound **15A** in acetic acid. The vials were then sealed and heated at 110°C for 10 h. Upon cooling to 25°C, the solutions were transferred by robot to filter tubes with a medium pore frit.
- 10 Nitrogen was then blown into the tubes to remove the acetic acid. A 1.0 mL portion of methylene chloride and 0.5 g of silica gel were then added to the tubes and they were shaken for 30 minutes. The tubes were drained into pre-tared custom microtubes. A 1.5 mL portion of 10% ethyl acetate in methylene chloride was then added to the filter tubes and they were 15 again shaken for 15 minutes and drained as before. Each tube was assayed for product purity (analytical LC) and identity (LC-MS). The tubes were then concentrated *in vacuo* and weighed for yields. The tube containing the reaction of 4-methyl-3-fluoroaniline and compound **15A**, yielded 0.0161 g of compound **51** as a white solid. HPLC: 85% at 2.43 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 302.23 [M+H]⁺. Of the remaining 95 additional reactions run, a total of 80 final compounds were obtained in >70% purity and >5 mg yield. Several samples needed further 20 purification which was performed by short SiO₂ column eluting with methylene chloride/acetone.
- 25

Examples 52 to 182

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Example 52 to 182 have the
5 following structure:



where -L-G, the compound name, retention time, molecular mass (provided for
10 certain compounds in the "Retention Time" column), and the procedure employed, are set forth in **Table 1**.

The chromatography techniques used to determine the compound retention times of **Table 1** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over

15 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

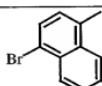
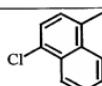
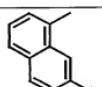
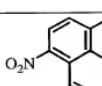
LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

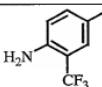
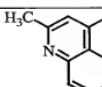
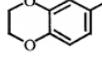
20 The molecular mass of the compounds listed in **Table 1**, where provided, were determined by MS (ES) by the formula m/z.

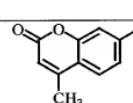
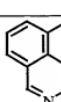
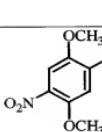
TABLE 1

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
52		(3a α ,4 α ,7 α ,7a α)-2-(2-Fluorenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.26 LC	51
53		(3a α ,4 α ,7 α ,7a α)-2-(1H-Benzotriazol-5-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.82 LC	51
54		(3a α ,4 α ,7 α ,7a α)-2-[3-Chloro-4-(4-morpholinyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.82 LC	51
55		(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-1H-inden-5-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-	3.50 LC	51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		isoindole-1,3(2H)-dione.		
56		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)\text{-}2\text{-}(4\text{-Bromo-1-naphthalenyl})\text{-}3\alpha,4,7,7\alpha\text{-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	3.25	51
57		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)\text{-}2\text{-}(4\text{-Chloro-1-naphthalenyl})\text{-}3\alpha,4,7,7\alpha\text{-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	3.11	51
58		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)\text{-}3\alpha,4,7,7\alpha\text{-Tetrahydro-2-(7-hydroxy-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	2.04 & 2.40	51
59		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)\text{-}3\alpha,4,7,7\alpha\text{-Tetrahydro-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	2.77 & 2.86	51

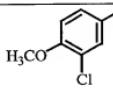
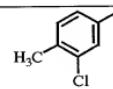
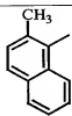
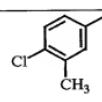
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	LC	
60		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(1H-indol-5-yl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.20	51
61		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(1H-indazol-6-yl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.08	51
62		(3a α ,4 α ,7 α ,7a α)-2-(1,3-Benzodioxol-5-yl)-3a,4,7,7a-Tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.33	51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
63		(3a α ,4 α ,7 α ,7a α)-2-[4-Amino-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	51	
64		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-methyl-4-quinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	0.913	LC
65		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(8-quinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.98	LC
66		(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.27	LC

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		isoindole-1,3(2H)-dione.		
67		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - $3a,4,7,7a$ - Tetrahydro-2-(4- methyl-2-oxo-2H-1- benzopyran-7-yl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	2.37	51
68		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - $3a,4,7,7a$ - Tetrahydro-2-(5- isoquinolinyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	1.49 LCMS	51
69		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - 2 - $(2,5$ -Dimethoxy-4- nitrophenyl)- $3a,4,7,7a$ -tetrahydro- $4,7$ -methano-1H- isoindole-1,3(2H)- dione.	2.39 LC	51

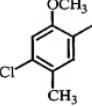
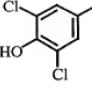
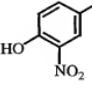
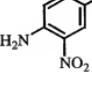
Ex. No.	<u>L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
70		$(3\alpha,4\alpha,7\alpha,7a\alpha)$ - 2,3,5,6-Tetrafluoro-4- (1,3,3a,4,7,7a- hexahydro-1,3-dioxo- 4,7-methano-2H- isoindol-2- yl)benzonitrile.		51
71		$(3\alpha,4\alpha,7\alpha,7a\alpha)$ - 3a,4,7,7a- Tetrahydro-2-(2,4,5- trifluorophenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	2.77 LC	51
72		$(3\alpha,4\alpha,7\alpha,7a\alpha)$ - 3a,4,7,7a- Tetrahydro-2-(2,4,5- trichlorophenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.		51
73		$(3\alpha,4\alpha,7\alpha,7a\alpha)$ - 2-(3,4-Difluorophenyl)- 3a,4,7,7a-tetrahydro- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.66 LC	51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
74		$(3a\alpha,4a,7\alpha,7a\alpha)$ -2-(2,3-Dihydro-1H-indol-6-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		51
75		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(3-Chloro-4-fluorophenyl)-3a,4,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.12 LCMS	51
76		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(3,4-Dichlorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.27 LC	51
77		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-(3,4,5-trichlorophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		51

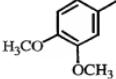
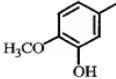
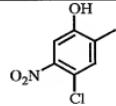
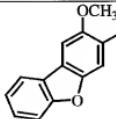
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
78		(3a α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.75 LC	51
79		(3a α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.68 LC	51
80		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-methyl-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.91 LC	51
81		(3a α ,4 α ,7 α ,7a α)-2-(4-Chloro-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-	2.81 LC	51

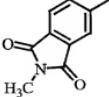
Ex. No.	<u>-L-G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure of <u>Example</u>
		isoindole-1,3(2H)-dione.		
82		(3a α ,4 α ,7 α ,7a α)-2-(3,4-dimethylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.86 LC	51
83		(3a α ,4 α ,7 α ,7a α)-2-[4-bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.38 LCMS	51
84		(3a α ,4 α ,7 α ,7a α)-2-(4-bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.21 LC	51
85		(3a α ,4 α ,7 α ,7a α)-2-(4-fluoro-3-nitrophenyl)-	2.62 LC	51

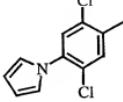
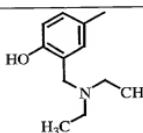
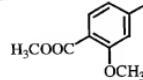
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		
86		(3a α ,4 α ,7 α ,7a α)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.89 LC	51
87		(3a α ,4 α ,7 α ,7a α)-2-(4-Chloro-3-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.96 LC	51
88		(3a α ,4 α ,7 α ,7a α)-2-[4-Chloro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
89	 <p>Chemical structure of 2-methoxy-5-methyl-4-chlorobiphenyl: A biphenyl system where the para position of the outer ring is substituted with a methoxy group (OCH₃), the meta position is substituted with a methyl group (CH₃), and the para position of the inner ring is substituted with a chlorine atom (Cl).</p>	<p>(3aα,4α,7α,7aα)-2-(4-Chloro-2-methoxy-5-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.</p>	3.05	51
90	 <p>Chemical structure of 3,5-dichloro-4-hydroxybiphenyl: A biphenyl system where the para position of the outer ring is substituted with a hydroxyl group (OH), the meta position is substituted with a chlorine atom (Cl), and the para position of the inner ring is substituted with a chlorine atom (Cl).</p>	<p>(3aα,4α,7α,7aα)-2-(3,5-Dichloro-4-hydroxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.</p>	2.98	51
91	 <p>Chemical structure of 3-hydroxy-4-nitro-5-nitrophenyl: A biphenyl system where the para position of the outer ring is substituted with a hydroxyl group (OH) and a nitro group (NO₂), and the meta position is substituted with a nitro group (NO₂).</p>	<p>(3aα,4α,7α,7aα)-3a,4,7,7a-Tetrahydro-2-(4-hydroxy-3-nitrophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.</p>	2.56	51
92	 <p>Chemical structure of 3-amino-4-nitrophenyl: A biphenyl system where the para position of the outer ring is substituted with an amino group (H₂N) and a nitro group (NO₂), and the meta position is substituted with a nitro group (NO₂).</p>	<p>(3aα,4α,7α,7aα)-2-(4-Amino-3-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.</p>	2.37	51

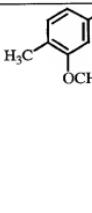
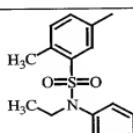
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		isoindole-1,3(2H)-dione.		
93		(3a α ,4 α ,7 α ,7a α)-2,2'- (2,3,5,6-Tetramethyl- 1,4- phenylene)bis[3a,4,7, 7a-tetrahydro-4,7- methano-1H- isoindole-1,3(2H)- dione].	2.19 LC	51
94		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(4- methyl-3- nitrophenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	2.80 LC	51
95		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(3,4,5- trimethoxyphenyl)- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.33 LC	51

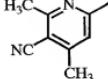
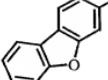
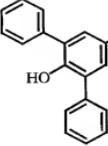
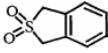
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
96	 <chem>Oc1ccc(Oc2ccccc2)cc1</chem>	$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(3,4-Dimethoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		51
97	 <chem>Oc1ccc(O)cc1</chem>	$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-(3-hydroxy-4-methoxyphenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.00 LC	51
98	 <chem>Oc1ccc(Cl)c([N+](=O)[O-])cc1</chem>	$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(5-Chloro-2-hydroxy-4-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.94 LC	51
99	 <chem>Oc1ccc2c(c1)oc3ccccc23</chem>	$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-(2-methoxy-3-dibenzofuranyl)-4,7-	2.78 LC	51

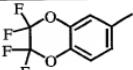
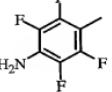
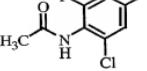
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		methano-1H- isoindole-1,3(2H)- dione.		
100	 <p>Chemical structure of 3,4-difluorobiphenyl: A biphenyl ring system with two fluorine atoms at the 3 and 4 positions.</p>	(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(2,3,4- trifluorophenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.		51
101	 <p>Chemical structure of 2,3-dihydro-2-methyl-1,3-dioxo-1H-isoindol-5-yl-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione: A complex heterocyclic compound featuring a fused five-membered ring system with a methyl group and two carbonyl groups.</p>	(3a α ,4 α ,7 α ,7a α)-2- (2,3-Dihydro-2- methyl-1,3-dioxo-1H- isoindol-5-yl)- 3a,4,7,7a-tetrahydro- 4,7-methano-1H- isoindole-1,3(2H)- dione.		51
102	 <p>Chemical structure of 2-bromo-3,4,5,6-tetrafluorobiphenyl: A biphenyl ring system with a bromine atom at the 2 position and four fluorine atoms at the 3, 4, 5, and 6 positions.</p>	(3a α ,4 α ,7 α ,7a α)-2-(4- Bromo-2,3,5,6- tetrafluorophenyl)- 3a,4,7,7a-tetrahydro- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.43 LC	51

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
103		(3a α ,4 α ,7 α ,7a α)-2-[2,5-Dichloro-4-(1H-pyrrol-1-yl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		51
104		(3a α ,4 α ,7 α ,7a α)-2-[3-[(Diethylamino)methyl]-4-hydroxyphenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.42 LC	51
105		(3a α ,4 α ,7 α ,7a α)-2-(6-Benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.44 LC	51
106		(3a α ,4 α ,7 α ,7a α)-4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-2-methoxybenzenecarboxylic acid, methyl	2.23 LC	51

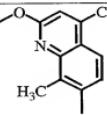
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		ester.		
107		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(2-oxo- 2H-1-benzopyran-6- yl)-4,7-methano-1H- isoindole-1,3(2H)- dione.	2.49 LC	51
108		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(2- methyl-8-quinolinyl)- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.21 LC	51
109		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2- (2,3,5,6-tetramethyl- 4-nitrophenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.		51
110		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(2,4,5- trimethylphenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	3.10 LC	51

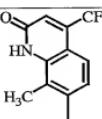
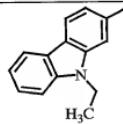
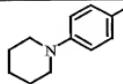
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		methano-1H- isoindole-1,3(2H)- dione.		
111		(3a α ,4 α ,7 α ,7a α)-2-(4- Fluoro-3- methylphenyl)- 3a,4,7,7a-tetrahydro- 4,7-methano-1H- isoindole-1,3(2H)- dione.		51
112		(3a α ,4 α ,7 α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(3- methoxy-4- methylphenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.		51
113		(3a α ,4 α ,7 α ,7a α)-N- Ethyl-5- (1,3,3a,4,7,7a- hexahydro-1,3-dioxo- 4,7-methano-2H- isoindol-2-yl)-2- methyl-N- phenylbenzenesulfon amide	2.75 LC	51

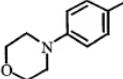
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
114		(3a α ,4 α ,7 α ,7a α)-6-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-2,4-dimethyl-3-pyridinecarbonitrile.	51	
115		(3a α ,4 α ,7 α ,7a α)-2-(3-Dibenzofuranyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.21 LC	51
116		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2'-hydroxy[1,1':3',1''-terphenyl]-5'-yl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	51	
117		(3a α ,4 α ,7 α ,7a α)-2-(1,3-Dihydro-2,2-dioxidobenzoc[<i>c</i>]thiophen-5-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-	3.31 LC	51

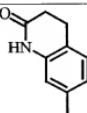
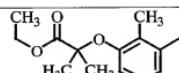
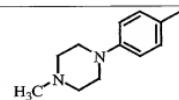
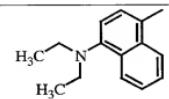
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		isoindole-1,3(2H)-dione.		
118		$(3\alpha,4\alpha,7\alpha,7\alpha\text{-})$ $3\alpha,4,7,7\text{-a-}$ Tetrahydro-2- $(2,2,3,3\text{-tetrafluoro-}$ $2,3\text{-dihydro-1,4-}$ $\text{benzodioxin-6-yl})\text{-}4,7\text{-}$ methano-1H- isoindole-1,3(2H)-dione.	2.16 LC	51
119		$(3\alpha,4\alpha,7\alpha,7\alpha\text{-})\text{-}2\text{-}(4\text{-}}$ Amino-2,3,5,6- $\text{tetrafluorophenyl})\text{-}$ $3\alpha,4,7,7\text{a-tetrahydro-}$ $4,7\text{-methano-1H-}$ isoindole-1,3(2H)-dione.	1.82 LC	51
120		$(3\alpha,4\alpha,7\alpha,7\alpha\text{-})\text{-}N\text{-}[2\text{-Chloro-6-fluoro-4-}$ $(1,3,3\alpha,4,7,7\text{a-}$ $\text{hexahydro-1,3-dioxo-}$ $4,7\text{-methano-2H-}$ isoindol-2- $\text{yl)phenyl]acetamide.}$	1.94 & 2.03 LC	51

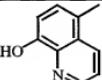
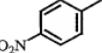
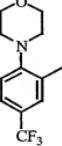
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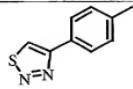
Ex. No.	<u>-L-G</u>	Compound <u>Name</u>	Retention Time Min.	Procedure of <u>Example</u>
121		(3a α ,4 α ,7 α ,7a α)-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile.	3.04 LC	51
122		(3a α ,4 α ,7 α ,7a α)-2-fluoro-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzonitrile.		51
123		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.04 LC	25D or 38A
124		(3a α ,4 α ,7 α ,7a α)-2-[2-Ethoxy-8-methyl-4-(trifluoromethyl)-7-quinolinyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	417.0 [M+H] ⁺	25D or 38A

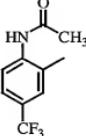
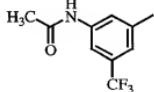
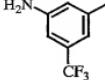
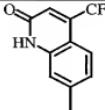
Ex. No.	<u>-L-G</u>	Compound <u>Name</u>	Retention Time Min.	Procedure of <u>Example</u>
		isoindole-1,3(2H)-dione.		
125		$(3a\alpha,4\alpha,7\alpha,7a\alpha)-2-[1,2\text{-Dihydro-8-methyl-2-oxo-4-(trifluoromethyl)-7-quinolinyl}]-3a,4,7,7a\text{-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	389.0 [M+H] ⁺	25D or 38A
126		$(3a\alpha,4\alpha,7\alpha,7a\alpha)-2-(9\text{-Ethyl-9H-carbazol-2-yl})-3a,4,7,7a\text{-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	7.25 LCMS 357.0 [M+H] ⁺	25D or 38A
127		$(3a\alpha,4\alpha,7\alpha,7a\alpha)-3a,4,7,7a\text{-Tetrahydro-2-[4-(1-piperidinyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.}$	3.66 LCMS 323.0 [M+H] ⁺	25D or 38A

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
128		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)$ - $3\alpha,4,7,7\alpha$ - Tetrahydro-2-[4-(4- morpholinyl)phenyl]- 4,7-methano-1H- isoindole-1,3(2H)- dione.	4.89 LCMS 325.0 $[\text{M}+\text{H}]^+$	25D or 38A
129		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)$ - $3\alpha,4,7,7\alpha$ - Tetrahydro-2-(7- quinolinyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	3.47 LCMS 291.0 $[\text{M}+\text{H}]^+$	25D or 38A
130		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)$ - Chlorophenyl)- $3\alpha,4,7,7\alpha$ -tetrahydro- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.84 LC	25D or 38A
131		$(3\alpha,4\alpha,7\alpha,7\alpha\alpha)$ - $3\alpha,4,7,7\alpha$ - Tetrahydro-2-(2- naphthalenyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	3.48 LC	25D or 38A

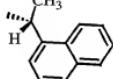
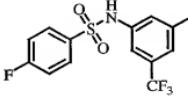
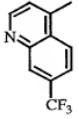
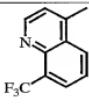
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
132		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - $3a,4,7,7a$ - Tetrahydro-2- $(1,2,3,4$ -tetrahydro-2- oxo-7-quinolinyl)-4,7- methano-1H- isoindole-1,3(2H)- dione.	2.69 LCMS 309.0 $[M+H]^+$	25D or 38A
133		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - $2-[3-(1,3,3a,4,7,7a$ - Hexahydro-1,3-dioxo- 4,7-methano-2H- isoindol-2-yl)-2- methylphenoxy]-2- methylpropanoic acid, ethyl ester.	6.82 & 6.93 LCMS 384.0 $[M+H]^+$	25D or 38A
134		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - $3a,4,7,7a$ - Tetrahydro-2-[4-(4- methyl-1- piperazinyl)phenyl]- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.13 LCMS 338.0 $[M+H]^+$	25D or 38A
135		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ - $2-[4-(Diethylamino)-1-$ naphthalenyl]- 4,7-methano-1H- isoindole-1,3(2H)- dione.	4.37 & 4.85 LCMS	25D or

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	361.0 [M+H] ⁺	38A
136		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(8-hydroxy-5-quinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.80 LC 307.2 [M+H] ⁺	25D or 38A
137		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-nitrophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.07 LC	25D or 38A
138		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-[2-(4-morpholinyl)-5-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.65 LC 393.2 [M+H] ⁺	25D or 38A

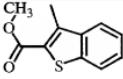
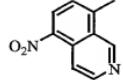
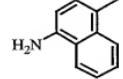
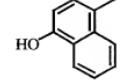
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
139		(3a α ,4a α ,7a α ,7a α)-2-(3,5-Dichlorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.95	25D or 38A
140		(3a α ,4a α ,7a α ,7a α)-2-(3-Chloro-4-fluorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.01	25D or 38A
141		(3a α ,4a α ,7a α ,7a α)-2-(4-Fluorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
142		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-[4-(1,2,3-thiadiazol-4-yl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A

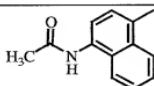
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
143		(3a α ,4 α ,7 α ,7a α)-N-[2-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-4-(trifluoromethyl)phenyl]acetamide.	3.34	25D or 38A
144		(3a α ,4 α ,7 α ,7a α)-N-[5-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-3-(trifluoromethyl)phenyl]acetamide.	3.34	25D or 38A
145		(3a α ,4 α ,7 α ,7a α)-2-[3-Amino-5-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.70	25D or 38A
146		(3a α ,4 α ,7 α ,7a α)-2-[1,2-Dihydro-2-oxo-4-(trifluoromethyl)-7-quinolinyl]-3a,4,7,7a-tetrahydro-4,7-dione.	3.55	25D or 38A

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		methano-1H-isoindole-1,3(2H)-dione.		
147		(3a α ,4 α ,7 α ,7a α)-N-[5-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-6-(methylthio)-8-quinoliny]acetamide	3.17 LC 394.2 [M+H] ⁺	25D or 38A
148		(3a α ,4 α ,7 α ,7a α)-2-[5-Ethoxy-2-(methoxymethyl)-4-(4-morpholinyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.25 LC 413.2 [M+H] ⁺	25D or 38A
149		(3a α ,4 α ,7 α ,7a α)-2-[(1R)-1-(naphthalenyl)ethyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.57 LCMS 318.1 [M+H] ⁺	25D or 38A

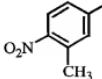
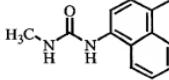
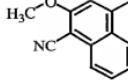
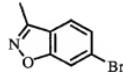
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
150		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-[(1S)-1-(1-naphthalenyl)ethyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.55 LCMS 318.2 [M+H] ⁺	25D or 38A
151		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -4-Fluoro-N-[3-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-5-(trifluoromethyl)phenyl]benzenesulfonamide.	3.78 LC 481.1 [M+H] ⁺	25D or 38A
152		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-[7-(trifluoromethyl)-4-quinolinyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.00 LCMS	25D or 38A
153		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-[8-(trifluoromethyl)-4-quinolinyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.73 LCMS	25D or

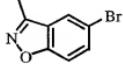
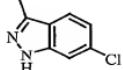
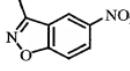
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		(trifluoromethyl)-4-quinolinyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		38A
154		(3a α ,4 α ,7 α ,7a α)-2-(3,4-Dimethyl-5-isoxazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.06 LCMS	25D or 38A
155		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-tetrahydro-2-(1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.99 LCMS	25D or 38A
156		(3a α ,4 α ,7 α ,7a α)-4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-1-naphthalenecarbonitrile.	2.66 2.79 LCMS	25D or 38A

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
157		(3a α ,4 α ,7a α ,7a α)-3- (1,3,3a,4,7,7a- Hexahydro-1,3-dioxo- 4,7-methano-2H- isoindol-2- yl)benzo[b]thiophene -2-carboxylic acid, methyl ester.	2.99 LC 354.0 [M+H] ⁺	25D or 38A
158		(3a α ,4 α ,7a α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(5- nitro-8- isoquinolinyl)-4,7- methano-1H- isoindole-1,3(2H)- dione, trifluoroacetate (1:1).	2.46 LC 336.0 [M+H] ⁺	25D or 38A
159		(3a α ,4 α ,7a α ,7a α)-2-(4- Amino-1- naphthalenyl)- 3a,4,7,7a-tetrahydro- 4,7-methano-1H- isoindole-1,3(2H)- dione.	1.96 & 2.30 LCMS	25D or 38A
160		(3a α ,4 α ,7a α ,7a α)- 3a,4,7,7a- Tetrahydro-2-(4- hydroxy-1-phenyl)- 4,7-methano-1H- isoindole-1,3(2H)- dione.	2.22 & 2.49 LCMS	25D or

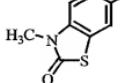
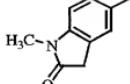
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		hydroxy-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	38A	
161		(3 α ,4 α ,7 α ,7a α)-3 α ,4,7,7a-Tetrahydro-2-(3-methylphenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.53 LC	25D or 38A
162		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromophenyl)-3 α ,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.89 LCMS	25D or 38A
163		(3 α ,4 α ,7 α ,7a α)-4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzonitrile.	2.34 LC	25D or 38A
164		(3 α ,4 α ,7 α ,7a α)-N-[4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzyl]propanamide.	2.04 & 2.26 LC	25D or

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		4,7-methano-2H- isoindol-2-yl)-1- naphthalenyl]acetam ide.		38A
165		(3a α ,4 α ,7 α ,7a α)-N-[4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-1-naphthalenyl]methanesulfonamide.	2.15 & 2.33 LC	25D or 38A
166		(3a α ,4 α ,7 α ,7a α)-2-(5-Bromo-8-isoquinolinyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.60 LC 370.0 [M+H] $^{+}$	25D or 38A
167		(3a α ,4 α ,7 α ,7a α)-2-(7,8-Dichloro-5-quinolinyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.76 & 3.06 LC 359.0 [M+H] $^{+}$	25D or 38A

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
168		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(3-methyl-4-nitrophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.75	LCMS 25D or 38A
169		(3a α ,4 α ,7 α ,7a α -N-[4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-1-naphthalenyl]-N'-methylurea.	2.07 & 2.25	LC 25D or 38A
170		(3a α ,4 α ,7 α ,7a α -4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-2-methoxy-1-naphthalenecarbonitrile.	2.82	LC 25D or 38A
171		(3a α ,4 α ,7 α ,7a α -2-(6-bromo-1,2-benzisoxazol-3-yl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione.	3.19 349.0 [M+H] $^+$	LCMS 25D or 38A

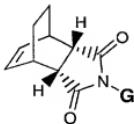
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		4,7-methano-1H-isoindole-1,3(2H)-dione.		
172		(3ac,4o,7a,7ao)-2-(5-Bromo-1,2-benzisoxazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.12	LCMS 25D 359.0 or [M+H] ⁺ 38A
173		(3ac,4o,7a,7ao)-2-(4-Fluoro-1H-indazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.42	LCMS 25D 298.3 or [M+H] ⁺ 38A
174		(3ac,4o,7a,7ao)-2-(6-Chloro-1H-indazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.84	LCMS 25D 313.0 or [M+H] ⁺ 38A
175		(3ac,4o,7a,7ao)-3a,4,7,7a-Tetrahydro-2-(5-nitro-3-methyl-2H-1,2-benzisoxazol-3-yl)-3-acetyl-4,7-dihydro-1H-isoindole-1,3(2H)-dione.	2.79	LC 25D or

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		nitro-1,2-benzisoxazol-3-yl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		38A
176		(3a α ,4 α ,7 α ,7a α)-3-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-2-benzofurancarboxylic acid, methyl ester.	2.91 LCMS 337.0 [M+H] ⁺	25D or 38A
177		(3a α ,4 α ,7 α ,7a α)-2-(3-Benzofuranyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.80 LCMS 279.0 [M+H] ⁺	25D or 38A
178		(3a α ,4 α ,7 α ,7a α)-2-(4-Chlorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.76 LC	25D or 38A
179		(3a α ,4 α ,7 α ,7a α)-Hexahydro-2-[3-methoxy-4-(1H-1,2,4-oxadiazol-5-yl)-phenyl]-1H-1,2,4-oxadiazol-5-yl.	2.41 LC	25D or

Ex. <u>No.</u>	<u>-L-G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure of <u>Example</u>
		triazol-1-yl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		38A
180		(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-2-oxo-6-benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.13 LC	25D or 38A
181		(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-3-methyl-2-oxo-6-benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.61 LC	25D or 38A
182		(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-1-methyl-2-oxo-1H-indol-5-yl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.68 LC	25D or 38A

Examples 183 to 271

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 183 to 271 have 5 the following structure:



- 10 where G, the compound name, retention time, and the procedure employed, are set forth in **Table 2** (L is a bond for the compounds of **Table 2**).

The chromatography techniques used to determine the compound retention times of **Table 2** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over

- 15 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

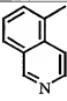
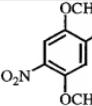
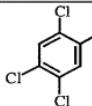
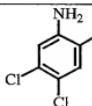
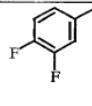
- 20 The molecular mass of the compounds listed in **Table 2**, where provided, were determined by MS (ES) by the formula m/z.

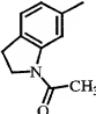
Table 2

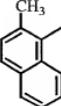
Ex. No.	<u>L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
183		(3 α ,4 α ,7 α ,7a α)-2-(2-Fluorenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.48	LCMS 51
184		(3 α ,4 α ,7 α ,7a α)-2-(1H-Benzotriazol-5-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.52	LCMS 51
185		(3 α ,4 α ,7 α ,7a α)-2-[3-Chloro-4-(4-morpholinyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.88	LCMS 51
186		(3 α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-1H-inden-5-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.98	LCMS 51
187		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-1-naphthalenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.19	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of <u>Example</u>
188		(3a α ,4a α ,7a α ,7a α)-2-(4-Chloro-1-naphthalenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.21 LCMS	51
189		(3a α ,4a α ,7a α ,7a α)-2-(5-Amino-1-naphthalenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.07 LCMS	51
190		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(7-hydroxy-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.57 LCMS	51
191		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-nitro-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.76 LCMS	51
192		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(1H-indol-5-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.93 LCMS	51
193		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(1H-indazol-6-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.79 LCMS	51
194		(3a α ,4a α ,7a α ,7a α)-2-(1,3-Benzodioxol-5-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.02 LCMS	51

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
		isoindole-1,3(2H)-dione.		
195		(3a α ,4 α ,7 α ,7a α)-2-[4-Amino-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.36	LCMS 51
196		(3a α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-iodophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.46	LCMS 51
197		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(8-quinoliny)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.72	LCMS 51
198		(3a α ,4 α ,7 α ,7a α)-2-(1,4-Benzodioxin-6-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.11	LCMS 51
199		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-[2-oxo-4-(trifluoromethyl)-2H-1-benzopyran-7-yl]-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.14	LCMS 51
200		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.24	LCMS 51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		1,3(2H)-dione.		
201		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-(5-isoquinolinyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	0.56	LCMS
202		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(2,5-Dimethoxy-4-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.21	LCMS
203		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-(2,4,5-trifluorophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.56	LCMS
204		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -3a,4,7,7a-Tetrahydro-2-(2,4,5-trichlorophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.45	LCMS
205		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(2-Amino-4,5-dichlorophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.79	LCMS
206		$(3a\alpha,4\alpha,7\alpha,7a\alpha)$ -2-(3,4-Difluorophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.57	LCMS

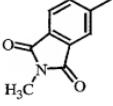
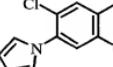
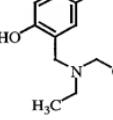
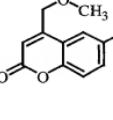
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
207		(3a α ,4a α ,7a α ,7a α)-1-Acetyl-6-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-2,3-dihydro-1H-indole.	1.82 LCMS	51
208		(3a α ,4a α ,7a α ,7a α)-(3-Chloro-4-fluorophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.89 LCMS	51
209		(3a α ,4a α ,7a α ,7a α)-2-(3,4-Dichlorophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.31 LCMS	51
210		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(3,4,5-trichlorophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.92 LCMS	51
211		(3a α ,4a α ,7a α ,7a α)-2-(3-Chloro-4-methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.6 LCMS	51
212		(3a α ,4a α ,7a α ,7a α)-2-(3-Chloro-4-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.1 LCMS	51

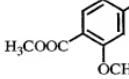
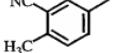
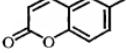
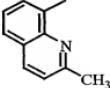
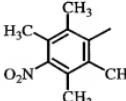
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
213		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-tetrahydro-2-(2-methyl-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.78	LCMS 51
214		(3a α ,4 α ,7 α ,7a α)-2-(4-Chloro-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.09	LCMS 51
215		(3a α ,4 α ,7 α ,7a α)-2-(3,4-Dimethylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.74	LCMS 51
216		(3a α ,4 α ,7 α ,7a α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.53	LCMS 51
217		(3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.2	LCMS 51
218		(3a α ,4 α ,7 α ,7a α)-2-(4-Fluoro-3-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.44	LCMS 51

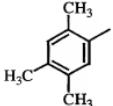
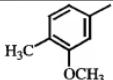
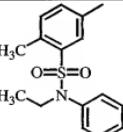
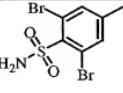
Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
219		(3a α ,4 α ,7 α ,7a α)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.15	LCMS 51
220		(3a α ,4 α ,7 α ,7a α)-2-(4-Chloro-3-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.87	LCMS 51
221		(3a α ,4 α ,7 α ,7a α)-2-[4-Chloro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.5	LCMS 51
222		(3a α ,4 α ,7 α ,7a α)-2-(4-Chloro-2-methoxy-5-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.91	LCMS 51
223		(3a α ,4 α ,7 α ,7a α)-2-(3,5-Dichloro-4-hydroxyphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.48	LCMS 51
224		(3a α ,4 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-hydroxy-3-nitrophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.2	LCMS 51

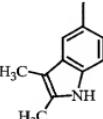
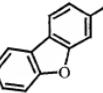
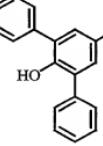
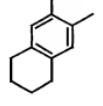
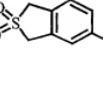
Ex. <u>No.</u>	<u>-L-G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure of <u>Example</u>
		isoindole-1,3(2H)-dione.		
225		(3 α ,4 α ,7 α ,7a α)-2-(4-Amino-3-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.9	LCMS
226		(3 α ,4 α ,7 α ,7a α)-2-(4-Amino-2,3,5,6-tetramethylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.3	LCMS
227		(3 α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-methyl-3-nitrophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.65	LCMS
228		(3 α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(3,4,5-trimethoxyphenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.01	LCMS
229		(3 α ,4 α ,7 α ,7a α)-2-(3,4-Dimethoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.83	LCMS
230		(3 α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(3-hydroxy-4-methoxyphenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.54	LCMS

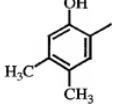
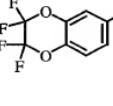
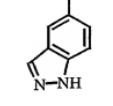
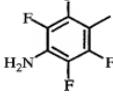
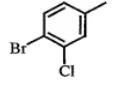
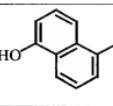
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		1H-isoindole-1,3(2H)-dione.		
231		(3a α ,4a α ,7a α)-6-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-1,4(2H,3H)-phthalazinedione.	1.68	LCMS
232		(3a α ,4a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-methyl-5-nitro-2-pyridinyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.99	LCMS
233		(3a α ,4a α ,7a α)-2-Chloro-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)- α -phenylbenzeneacetonitrile.	3.44	LCMS
234		(3a α ,4a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-methoxy-3-dibenzofuranyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.34	LCMS
235		(3a α ,4a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2,3,4-trifluorophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.82	LCMS

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
236		(3a α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-2-methyl-1,3-dioxo-1H-isoindol-5-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.24	LCMS 51
237		(3a α ,4 α ,7 α ,7a α)-2-[2,5-Dichloro-4-(1H-pyrrol-1-yl)phenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.61	LCMS 51
238		(3a α ,4 α ,7 α ,7a α)-2-[3-[(Diethylamino)methyl]-4-hydroxyphenyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	0.8	LCMS 51
239		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-[4-(methoxymethyl)-2-oxo-2H-1-benzopyran-7-yl]-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.34	LCMS 51
240		(3a α ,4 α ,7 α ,7a α)-2-(6-Benzothiazolyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.04	LCMS 51

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
241		(3a α ,4 α ,7 α ,7a α)-4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-2-methoxybenzoic acid, methyl ester.	2.32	LCMS 51
242		(3a α ,4 α ,7 α ,7a α)-5-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-2-methylbenzonitrile.	2.38	LCMS 51
243		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-oxo-2H-1-benzopyran-6-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.93	LCMS 51
244		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-methyl-8-quinolinyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.45	LCMS 51
245		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2,3,5,6-tetramethyl-4-nitrophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.16	LCMS 51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
246		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4,5-trimethylphenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.92 LCMS	51
247		(3a α ,4 α ,7 α ,7a α)-2-(4-Fluoro-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.62 LCMS	51
248		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(3-methoxy-4-methylphenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.67 LCMS	51
249		(3a α ,4 α ,7 α ,7a α)-N-Ethyl-5-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-2-methyl-N-phenylbenzenesulfonamide.	3.35 LCMS	51
250		(3a α ,4 α ,7 α ,7a α)-2,6-Dibromo-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)benzenesulfonamide.	3.15 LCMS	51

Ex. No.	-L-G	Compound Name	Retention Time Min.	Procedure of Example
251		(3a α ,4a α ,8a α ,8a α)-2-(2,3-Dimethyl-1H-indol-5-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.59 LCMS	51
252		(3a α ,4a α ,7a α ,7a α)-2-(3-Dibenzofuranyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.52 LCMS	51
253		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2'-hydroxy[1,1':3',1"-terphenyl]-5'-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.51 LCMS	51
254		(3a α ,4a α ,7a α ,7a α)-3a,4,7,7a-Tetrahydro-2-(5,6,7,8-tetrahydro-3-hydroxy-2-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.86 LCMS	51
255		(3a α ,4a α ,7a α ,7a α)-2-(1,3-Dihydro-2,2-dioxido-benzo[c]thiophen-5-yl)-hexahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.39 LCMS	51

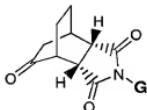
Ex. <u>No.</u>	<u>-L-G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure of <u>Example</u>
256		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-hydroxy-4,5-dimethylphenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.3 LCMS	51
257		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.63 LCMS	51
258		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(1H-indazol-5-yl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.61 LCMS	51
259		(3a α ,4 α ,7 α ,7a α)-2-(4-Amino-2,3,5,6-tetrafluorophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	2.36 LCMS	51
260		(3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-chlorophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.39 LCMS	51
261		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(5-hydroxy-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	1.87 LCMS	51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
		1H-isoindole-1,3(2H)-dione.		
262		(3a α ,4 α ,7 α ,7a α)-N-[2-Chloro-6-fluoro-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)phenyl]acetamide.	1.39	LCMS 51
263		(3a α ,4 α ,7 α ,7a α)-4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.03	LCMS 51
264		(3a α ,4 α ,7 α ,7a α)-5-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)-2-(4-morpholinyl)benzoic acid, methyl ester.	2.23	LCMS 51
265		(3a α ,4 α ,7 α ,7a α)-2-Fluoro-5-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-ethano-2H-isoindol-2-yl)benzonitrile.	2.23	LCMS 51
266		(3a α ,4 α ,7 α ,7a α)-2-(4-Bromophenyl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	5.96	LC 33

Ex. No.	<u>L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
267		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(2-naphthalenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	7.04 LC	33
268		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.81 LC	33
269		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-nitrophenyl)-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.46 LC	33
270		(3a α ,4 α ,8 α ,8a α)-2-(9-Ethyl-9H-carbazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	4.16 LC	33
271		(3a α ,4 α ,8 α ,8a α)-2-[1,2-Dihydro-8-methyl-2-oxo-4-(trifluoromethyl)-7-quinolinyl]-3a,4,7,7a-tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione.	3.60 & 3.97 LC	33

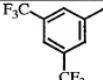
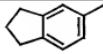
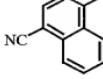
Examples 272 to 366

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 272 to 366 have
5 the following structure:



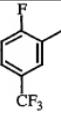
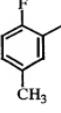
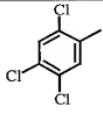
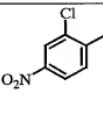
- where G, the compound name, retention time, and the procedure employed are set
10 forth in **Table 3** (L is a bond for the compounds of **Table 3**).
The chromatography techniques used to determine the compound retention times of **Table 3** are as follows:
LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.
The molecular mass of the compounds listed in **Table 3**, where provided, were
20 determined by MS (ES) by the formula m/z.

Table 3

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
272		(3 α ,4 α ,7 α ,7a α)-2-[3,5-Bis(trifluoromethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.29 LCMS	51
273		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.88 LCMS	51
274		(3 α ,4 α ,7 α ,7a α)-2-(2,3-Dihydro-1H-inden-5-yl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.63 LCMS	51
275		(3 α ,4 α ,7 α ,7a α)-4-(Octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)-1-naphthalenecarbonitrile.	2.47 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
276		(3 α ,4 α ,7 α ,7 α)-2-(4-Chloro-1-naphthalenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.02	LCMS 51
277		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-(4-nitro-1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.64	LCMS 51
278		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-(2-naphthalenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.65	LCMS 51
279		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-(5-quinolinyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.29	LCMS 51
280		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-(6-quinolinyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.12	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
281		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.11 LCMS	51
282		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(5-isoquinolinyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.04 LCMS	51
283		(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dinitrophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.37 LCMS	51
284		(3 α ,4 α ,7 α ,7a α)-2-(2,5-Dibromophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.58 LCMS	51
285		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(2,4,5-trifluorophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.24 LCMS	51

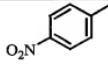
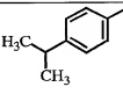
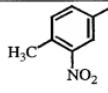
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		1,3,5(2H,4H)-trione.		
286		(3 α ,4 α ,7 α ,7a α)-2-[2-Fluoro-5-(trifluoromethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.62 LCMS	51
287		(3 α ,4 α ,7 α ,7a α)-2-(2-Fluoro-5-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.18 LCMS	51
288		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(2,4,5-trichlorophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.02 LCMS	51
289		(3 α ,4 α ,7 α ,7a α)-2-(2-Chloro-4-nitrophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.42 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
290		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-2-[2-Chloro-5-(trifluoromethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.67	LCMS
291		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-2-(3-Fluorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.02	LCMS
292		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-2-(3,4-Difluorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.26	LCMS
293		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-2-(3,5-Difluorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.30	LCMS
294		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-2-(3-Chlorophenyl)tetrahydro-4,7-ethano-1H-isoindole-	2.38	LCMS

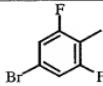
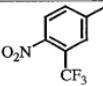
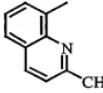
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		1,3,5(2H,4H)-trione.		
295		(3 α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-fluorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.56 LCMS	51
296		(3 α ,4 α ,7 α ,7a α)-2-(3,4-Dichlorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.89 LCMS	51
297		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(3,4,5-trichlorophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.37 LCMS	51
298		(3 α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.72 LCMS	51
299		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(3-iodophenyl)-4,7-	2.58 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethano-1H-isoindole-1,3,5(2H,4H)-trione.		
300		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(3-nitrophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.06 LCMS	51
301		(3 α ,4 α ,7 α ,7a α)-2-(3-Acetylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.86 LCMS	51
302		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.62 LCMS	51
303		(3 α ,4 α ,7 α ,7a α)-2-(3,4-Dimethylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.46 LCMS	51
304		(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dimethylphenyl)tetra	2.49 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		hydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.		
305		(3 α ,4 α ,7 α ,7a α)-2-(3-Ethylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.50 LCMS	51
306		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.53 LCMS	51
307		(3 α ,4 α ,7 α ,7a α)-2-(4-Fluoro-3-nitrophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.16 LCMS	51
308		(3 α ,4 α ,7 α ,7a α)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.80 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
309		(3 α ,4 α ,7 α ,7a α)-2-(4-Chloro-3-nitrophenyl)tetrahydrono-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.55 LCMS	51
310		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(4-iodophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.67 LCMS	51
311		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(4-nitrophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.12 LCMS	51
312		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-[4-(1-methylethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.86 LCMS	51
313		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(4-methyl-3-nitrophenyl)-4,7-ethano-1H-isoindole-	2.34 LCMS	51

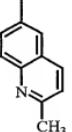
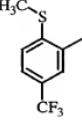
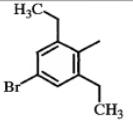
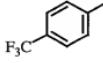
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		1,3,5(2H,4H)-trione.		
314		(3a α ,4 α ,7 α ,7a α)-4-(Octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)benzeneacetonitrile	1.68 LCMS	51
315		(3a α ,4 α ,7 α ,7a α)-2-(4-Ethylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.55 LCMS	51
316		(3a α ,4 α ,7 α ,7a α)-2-[4-(Acetoxyethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.25 LCMS	51
317		(3a α ,4 α ,7 α ,7a α)-Tetrahydro-2-(4-propylphenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.91 LCMS	51
318		(3a α ,4 α ,7 α ,7a α)-Tetrahydro-2-(2,3,4-trifluorophenyl)-4,7-ethano-1H-isoindole-	2.41 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		1,3,5(2H,4H)-trione.		
319		(3 α ,4 α ,7 α ,7 α)-2-(4-Bromo-2,6-difluorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.64 LCMS	51
320		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.81 LCMS	51
321		(3 α ,4 α ,7 α ,7 α)-2-(6-Benzothiazolyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.87 LCMS	51
322		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-(2-methyl-8-quinolinyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.01 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
323		(3 α ,4 α ,7 α ,7a α)-2-(4-Fluoro-3-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.37 LCMS	51
324		(3 α ,4 α ,7 α ,7a α)-2-(1,3-Dihydro-3-oxo-5-isobenzofuranyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.57 LCMS	51
325		(3 α ,4 α ,7 α ,7a α)-N-[2-Nitro-4-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)phenyl]acetamide.	1.87 LCMS	51
326		(3 α ,4 α ,7 α ,7a α)-2-(2-Ethyl-5-nitrophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.47 LCMS	51
327		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(2-methyl-5-benzofuranyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.50 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethano-1H-isoindole-1,3,5(2H,4H)-trione.		
328		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(1H-indazol-5-yl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.58 LCMS	51
329		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-chlorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.95 LCMS	51
330		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-[3-(trifluoromethoxy)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	4.36 LCMS	51
331		(3 α ,4 α ,7 α ,7a α)-4-(Octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile.	2.60 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
332		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-[2-(methylsulfonyl)-4-nitrophenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	1.64	LCMS 51
333		(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dibromophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.12	LCMS 51
334		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(3-iodo-4-methylphenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.86	LCMS 51
335		(3 α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-iodophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.99	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
336	 <p>Chemical structure of 2-methyl-6-quinolinyl: A quinolinyl ring system with a methyl group at the 2-position.</p>	<p>(3aa,4a,7a,7aa)-Tetrahydro-2-(2-methyl-6-quinolinyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.</p>	1.10	LCMS 51
337	 <p>Chemical structure of 2-(trifluoromethylthio)phenyl: A phenyl ring with a trifluoromethylthio group at the 2-position.</p>	<p>(3aa,4a,7a,7aa)-Tetrahydro-2-[2-(methylthio)-5-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.</p>	2.58	LCMS 51
338	 <p>Chemical structure of 2-bromo-6-diethylphenyl: A phenyl ring with a bromine atom at the 2-position and a diethylmethyl group at the 6-position.</p>	<p>(3aa,4a,7a,7aa)-2-(4-Bromo-2,6-diethylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.</p>	3.35	LCMS 51
339	 <p>Chemical structure of 2-(trifluoromethyl)phenyl: A phenyl ring with a trifluoromethyl group at the 2-position.</p>	<p>(3aa,4a,7a,7aa)-Tetrahydro-2-[4-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.</p>	2.71	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>	
340		(3a α ,4a α ,7a α ,7a α)-2-(4-Chloro-3-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.70	LCMS	51
341		(3a α ,4a α ,7a α ,7a α)-Tetrahydro-2-[4-(methoxymethyl)-2-oxo-2H-1-benzopyran-7-yl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.16	LCMS	51
342		(3a α ,4a α ,7a α ,7a α)-N-Methyl-3-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)benzamide.	1.54	LCMS	51
343		(3a α ,4a α ,7a α ,7a α)-2-(6-Acetyl-1,3-benzodioxol-5-yl)tetrahydro-4,7-ethano-1H-isindole-1,3,5(2H,4H)-trione.	1.90	LCMS	51
344		(3a α ,4a α ,7a α ,7a α)-Tetrahydro-2-(3,4,5-trifluorophenyl)-4,7-ethano-1H-isindole-1,3,5(2H,4H)-trione.	2.59	LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethano-1H-isoindole-1,3,5(2H,4H)-trione.		
345		(3 α ,4 α ,7 α ,7a α)-2-Bromo-5-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)benzoic acid, methyl ester.	2.51 LCMS	51
346		(3 α ,4 α ,7 α ,7a α)-2-(3-Chloro-4-nitrophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.55 LCMS	51
347		(3 α ,4 α ,7 α ,7a α)-2-[5-[(Difluoromethyl)sulfonyl]-2-methoxyphenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.02 LCMS	51
348		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.45 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
349		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-1-naphthalenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.07	LCMS
350		(3 α ,4 α ,7 α ,7a α)-2-(3,5-Dichlorophenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.97	LCMS
351		(3 α ,4 α ,7 α ,7a α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.10	LCMS
352		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.85	LCMS
353		(3 α ,4 α ,7 α ,7a α)-2-(4-Bromo-1-naphthalenyl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.62	LC

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		dro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.		
354		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-(1-naphthalenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.97	LC 13C
355		(3 α ,4 α ,7 α ,7 α)-Tetrahydro-2-[2-methyl-3-(trifluoromethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.35	LC 13C
356		(3 α α ,4 α ,7 α ,7 α)-2-(2,2-Difluoro-1,3-benzodioxol-5-yl)tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.20	LC 13C
357		(3 α ,4 α ,7 α ,7 α)-2-[4-(4-Chlorophenoxy)-2-(trifluoromethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	3.97	LC 13C

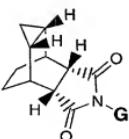
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
358		(3a α ,4 α ,7 α ,7a α)-2-Fluoro-5-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)benzonitrile.	2.55	LC
359		(3a α ,4 α ,7 α ,7a α)-2-Chloro-4-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)benzonitrile.	2.81	LC
360		(3a α ,4 α ,7 α ,7a α)-N-[4-(Octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)-2-(trifluoromethyl)phenyl]acetamide.	3.68	LC
361		(3a α ,4 α ,7 α ,7a α)-2-[4-(1,1-Dimethylethyl)-3-nitrophenyl]tetrahydr-0-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione	3.12	LC

362		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-(3-methyl-4-nitrophenyl)-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.40 LC	13C
363		(3 α ,4 α ,7 α ,7a α)-Tetrahydro-2-[3-(1-methylethyl)phenyl]-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.78 LC	13C
364		(3 α ,4 α ,7 α ,7a α)-N-(1,1-Dimethylethyl)-5-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)-1-naphthalenesulfonamide.	2.57 & 2.72 LC	13C
365		(3 α ,4 α ,7 α ,7a α)-2-[3-(1,1-Dimethylethyl)phenyl]tetrahydro-4,7-ethano-1H-isoindole-1,3,5(2H,4H)-trione.	2.99 LC	13C

366		(3ac,4 α ,7 α ,7a α)-N-Butyl-3-(octahydro-1,3,5-trioxo-4,7-ethano-2H-isoindol-2-yl)benzenesulfonamide.	2.52	LC	13C
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Examples 367 to 460

5 Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 367 to 460 have the following structure:



10

where G, the compound name, retention time, and the procedure employed are set forth in **Table 4** (L is a bond for the compounds of **Table 4**).

The chromatography techniques used to determine the compound retention times of **Table 4** are as follows:

- 15 **LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- LCMS*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.
- 20 The molecular mass of the compounds listed in **Table 4**, where provided, were determined by MS (ES) by the formula m/z.

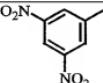
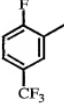
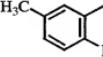
Table 4

<u>Ex. No.</u>	<u>L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
367		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3,4-Dichlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.69	LCMS 51
368		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(4-Bromo-3-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.64	LCMS 51
369		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(1-naphthalenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.22	LCMS 51
370		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(2-naphthalenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione	3.46	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		le-1,3(2H,3aH)-dione.		
371		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.45 LCMS	51
372		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(3,5-Dichlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.56 LCMS	51
373		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.55 LCMS	51
374		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-[3,5-Bis(trifluoromethyl)phenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.93 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		le-1,3(2H,3aH)-dione.		
375		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.67 LCMS	51
376		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(2,3-Dihydro-1H-inden-5-yl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.48 LCMS	51
377		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4-(Octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindol-2(1H)-yl)-1-naphthalenecarbonitrile.	3.15 LCMS	51
378		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(4-Bromo-1-naphthalenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.65 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of <u>Example</u>
379		(3 α ,4 β ,4 $\alpha\alpha$,5 $\alpha\alpha$,6 β ,6 $\alpha\alpha$)-2-(4-Chloro-1-naphthalenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.62	LCMS 51
380		(3 α ,4 β ,4 $\alpha\alpha$,5 $\alpha\alpha$,6 β ,6 $\alpha\alpha$)-4,4a,5,5a,6,6a-hexahydro-2-(5-quinolinyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.25	LCMS 51
381		(3 α ,4 β ,4 $\alpha\alpha$,5 $\alpha\alpha$,6 β ,6 $\alpha\alpha$)-4,4a,5,5a,6,6a-hexahydro-2-(6-quinolinyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.14	LCMS 51
382		(3 α ,4 β ,4 $\alpha\alpha$,5 $\alpha\alpha$,6 β ,6 $\alpha\alpha$)-4,4a,5,5a,6,6a-hexahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.97	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
383		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-hexahydro-2-(5-isoquinolinyl)-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	1.94	LCMS
384		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3,5-dinitrophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.38	LCMS
385		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-hexahydro-2-(2,4,5-trifluorophenyl)-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.26	LCMS
386		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-[2-fluoro-5-(trifluoromethyl)phenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.49	LCMS
387		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(2-fluoro-5-	3.19	LCMS

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		methylphenyl)- 4,4a,5,5a,6,6a- hexahydro-4,6- ethanocycloprop[f]isoindo- le-1,3(2H,3aH)-dione.		
388		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- 2-(2-Chloro-4- nitrophenyl)- 4,4a,5,5a,6,6a- hexahydro-4,6- ethanocycloprop[f]isoindo- le-1,3(2H,3aH)-dione.	2.40	LCMS 51
389		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- 2-[2-Chloro-5- (trifluoromethyl)phenyl]- 4,4a,5,5a,6,6a- hexahydro-4,6- ethanocycloprop[f]isoindo- le-1,3(2H,3aH)-dione.	3.48	LCMS 51
390		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- 2-(3-Fluorophenyl)- 4,4a,5,5a,6,6a- hexahydro-4,6- ethanocycloprop[f]isoindo- le-1,3(2H,3aH)-dione.	3.06	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	Retention Time Min.	Procedure of <u>Example</u>
391		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3,4-Difluorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.21	LCMS 51
392		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Fluoro-4-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.34	LCMS 51
393		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3,5-Difluorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.30	LCMS 51
394		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Chlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.32	LCMS 51

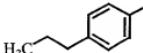
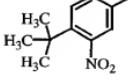
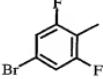
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
395		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Chloro-4-fluorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.43	LCMS 51
396		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(3,4,5-trichlorophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	4.07	LCMS 51
397		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Chloro-4-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.78	LCMS 51
398		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(3-iodophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.47	LCMS 51

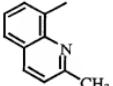
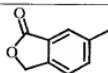
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
399		(3 α ,4 β ,4 α α ,5 α ,6 β ,6 α α)-4,4 α ,5,5 α ,6,6 α -Hexahydro-2-(3-nitrophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.0	LCMS
400		(3 α ,4 β ,4 α α ,5 α ,6 β ,6 α α)-2-(3-Acetylphenyl)-4,4 α ,5,5 α ,6,6 α -hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.81	LCMS
401		(3 α ,4 β ,4 α α ,5 α ,6 β ,6 α α)-2-(3,4-Dimethylphenyl)-4,4 α ,5,5 α ,6,6 α -hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.36	LCMS
402		(3 α ,4 β ,4 α α ,5 α ,6 β ,6 α α)-2-(3,5-Dimethylphenyl)-4,4 α ,5,5 α ,6,6 α -hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.38	LCMS
403		(3 α ,4 β ,4 α α ,5 α ,6 β ,6 α α)-4,4 α ,5,5 α ,6,6 α -Hexahydro-2-[3-	2.97	LCMS

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		(hydroxymethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
404		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(3-Ethylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.38	LCMS 51
405		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4-(Octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindole-2(1H)-yl)benzonitrile.	2.89	LCMS 51
406		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(4-Bromophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.43	LCMS 51
407		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.80	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>	
		le-1,3(2H,3aH)-dione.			
408		(3 α ,4 β ,4 α ,5 α ,6 β ,6a α)-2-(4-Fluoro-3-nitrophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.14	LCMS	51
409		(3 α ,4 β ,4 α ,5 α ,6 β ,6a α)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.55	LCMS	51
410		(3 α ,4 β ,4 α ,5 α ,6 β ,6a α)-2-(4-Chloro-3-nitrophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.42	LCMS	51
411		(3 α ,4 β ,4 α ,5 α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-iodophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.53	LCMS	51

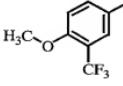
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		le-1,3(2H,3aH)-dione.		
412		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-nitrophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.12 LCMS	51
413		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-(1-methylethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.64 LCMS	51
414		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-methyl-3-nitrophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.28 LCMS	51
415		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4-(Octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindol-1-2(1H)-yl)benzeneacetonitrile.	2.67 LCMS	51
416		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(4-Ethylphenyl)-	3.44 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
417		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-(4-propylphenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.68	LCMS 51
418		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-(2,3,4-trifluorophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.44	LCMS 51
419		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-[4-(1,1-Dimethylethyl)-3-nitrophenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione	3.76	LCMS 51
420		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(4-Bromo-2,6-difluorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione	3.62	LCMS 51

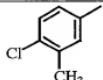
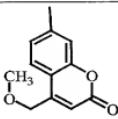
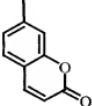
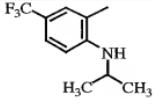
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
421		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(6-Benzothiazolyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.95	LCMS 51
422		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-(2-methyl-8-quinolinyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.95	LCMS 51
423		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(4-Fluoro-3-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.83	LCMS 51
424		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(1,3-Dihydro-3-oxo-5-isobenzofuranyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.54	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>	
		ethanocycloprop[f]isoindo le-1,3(2H,3aH)-dione.			
425		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- N-[2-Nitro-4-(octahydro- 1,3-dioxo-4,6- ethanocycloprop[f]isoindol- 1-2(1H)- yl)phenyl]acetamide.	2.85	LCMS	51
426		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- 2-(5-Acetyl-2-methyl-4- nitrophenyl)- 4,4a,5,5a,6,6a- hexahydro-4,6- ethanocycloprop[f]isoindol- 1,3(2H,3aH)-dione.	3.05	LCMS	51
427		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- 2-(2-Ethyl-5- nitrophenyl)- 4,4a,5,5a,6,6a- hexahydro-4,6- ethanocycloprop[f]isoindol- 1,3(2H,3aH)-dione.	3.28, 3.24	LCMS	51
428		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)- 4,4a,5,5a,6,6a- Hexahydro-2-(2-methyl- 5-benzofuranyl)-4,6- ethanocycloprop[f]isoindol- 1,3(2H,3aH)-dione.	3.33	LCMS	51

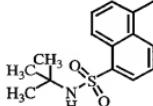
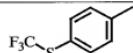
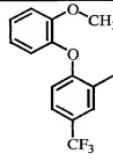
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		le-1,3(2H,3aH)-dione.		
429		(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(2,3-Dihydro-1-oxo-1H-inden-5-yl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	2.84	LCMS
430		(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-(1H-indazol-5-yl)-4,6-ethanocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	2.59	LCMS
431		(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-hexahydro-2-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4,6-ethanocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	3.53	LCMS
432		(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(4-Bromo-3-chlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	3.75	LCMS

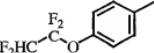
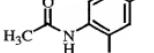
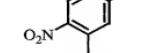
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethanocycloprop[f]isoindo le-1,3(2H,3aH)-dione.		
433		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)- 4,4a,5,5a,6,6a- Hexahydro-2-[3- (trifluoromethoxy)phenyl]-4,6- ethanocycloprop[f]isoindo le-1,3(2H,3aH)-dione.	3.55	LCMS 51
434		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)- 4-(Octahydro-1,3-dioxo- 4,6- ethanocycloprop[f]isoindo l-2(1H)-yl)-2- (trifluoromethyl)benzonit rile.	3.42	LCMS 51
435		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)- 4,4a,5,5a,6,6a- Hexahydro-2-[4-methoxy- 3- (trifluoromethyl)phenyl]- 4,6- ethanocycloprop[f]isoindo le-1,3(2H,3aH)-dione.	3.19	LCMS 51
436		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)- 2-(3,5-Dibromophenyl)- 4,4a,5,5a,6,6a-	3.93	LCMS 51

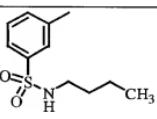
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
437		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(3-iodo-4-methylphenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.66	LCMS 51
438		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Chloro-4-iodophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.78	LCMS 51
439		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(2-methyl-6-quinolinyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	1.93	LCMS 51
440		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-(trifluoromethyl)phenyl]-4,6-	3.51	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
441		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(4-Chloro-3-methylphenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.57	LCMS 51
442		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-(methoxymethyl)-2-oxo-2H-1-benzopyran-7-yl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.03	LCMS 51
443		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(2-oxo-2H-1-benzopyran-6-yl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.76	LCMS 51
444		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-[2-[(1-methylethyl)amino]-5-	3.67	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
445		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Chloro-4-nitrophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.46	LCMS 51
446		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(3-methyl-4-nitrophenyl)-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.29	LCMS 51
447		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-[5-[(Difluoromethyl)sulfonyl]-2-methoxyphenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.81	LCMS 51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
448		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-hexahydro-2-[3-(1-methylethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.39	LC 6B
449		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-N-(1,1-Dimethylethyl)-5-(octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindole-1-2(1H)-yl)-1-naphthalenesulfonamide.	3.393	LC 6B
450		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-hexahydro-2-[4-[(trifluoromethyl)thiolophenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.57	LC 6B
451		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-hexahydro-2-[2-(2-methoxyphenoxy)-5-(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.88	LC 6B

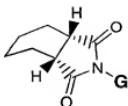
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
452		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-4,4a,5,5a,6,6a-hexahydro-2-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-4,6-ethanocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	3.23 LC	6B
453		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-N-[4-(Octahydro-1,3-dioxo-4,6-ethanocycloprop[fl]isoindole-1-2(1H)-yl)-2-(trifluoromethyl)phenyl]acetamide.	3.53 LC	6B
454		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-(3-Acetyl-4-nitrophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	2.91 LC	6B
455		(3 α ,4 β ,4 α ,5 α ,6 β ,6 α)-2-[3-(1,1-dimethylpropyl)phenyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethanocycloprop[fl]isoindole.	3.52 LC	6B

<u>Ex. No.</u>	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of <u>Example</u>
		le-1,3(2H,3aH)-dione.		
456		(3ac,4 β ,4ac,5ac,6 β ,6ac)-N-Butyl-3-(Octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindo-1-2(1H)-yl)benzenesulfonamide.	3.05	LC
457		(3ac,4 β ,4ac,5ac,6 β ,6ac)-4,4a,5,5a,6,6a-Hexahydro-2-[2-methyl-3-(trifluoromethyl)phenyl]-4,6-ethanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.24 &	3.42
458		(3ac,4 β ,4ac,5ac,6 β ,6ac)-2-Fluoro-5-(Octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindole-1-2(1H)-yl)benzonitrile.	2.74	LC
459		(3ac,4 β ,4ac,5ac,6 β ,6ac)-N-Methyl-3-(octahydro-1,3-dioxo-4,6-ethanocycloprop[f]isoindole-1-2(1H)-yl)benzamide.	2.52	LC

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
460		(3 α ,4 β ,4 α o,5 α o,6 β ,6 α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,6-ethanocycloprop[<i>f</i>]isoindole-1,3(2H,3aH)-dione.	3.30 & 3.40 *LCMS	6B

Examples 461 to 544

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 461 to 544 have the following structure:



where G, the compound name, retention time, and the procedure employed, are set

10 forth in **Table 5** (L is a bond for the compounds of **Table 5**).

The chromatography techniques used to determine the compound retention times of **Table 5** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

15 **LCMS*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

The molecular mass of the compounds listed in **Table 5**, where provided, were determined by MS (ES) by the formula m/z.

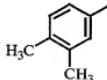
Table 5

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
461		2-(2-Fluorenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	0.98 LCMS	51
462		2-[3-Chloro-4-(4-morpholinyl)phenyl]hexahydro-1H-isoindole-1,3(2H)-dione.	0.23 LCMS	51
463		2-(2,3-Dihydro-1H-inden-5-yl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.17 LCMS	51
464		2-(4-Bromo-1-naphthalenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.30 LCMS	51
465		2-(4-Chloro-1-naphthalenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.26 LCMS	51
466		Hexahydro-2-(3-iodo-4-methylphenyl)-1H-isoindole-1,3(2H)-dione.	3.55 LCMS	51

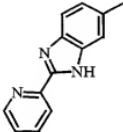
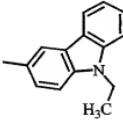
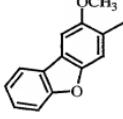
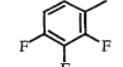
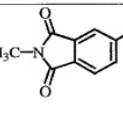
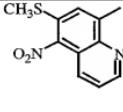
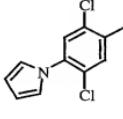
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
467		Hexahydro-2-(4-nitro-1-naphthalenyl)-1H-isoindole-1,3(2H)-dione.	3.09	51
468		Hexahydro-2-(1H-indol-5-yl)-1H-isoindole-1,3(2H)-dione.	2.66	51
469		Hexahydro-2-(5-quinolinyl)-1H-isoindole-1,3(2H)-dione.	2.03	51
470		Hexahydro-2-(1H-indazol-6-yl)-1H-isoindole-1,3(2H)-dione.	2.56	51
471		2-(1,3-Benzodioxol-5-yl)hexahydro-1H-isoindole-1,3(2H)-dione.	1.06	51
472		2-(3-Fluoro-4-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.06	51
473		Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-1H-isoindole-1,3(2H)-dione.	0.29	51
474		Hexahydro-2-(8-quinolinyl)-1H-isoindole-1,3(2H)-dione.	0.31	51

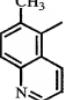
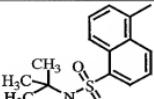
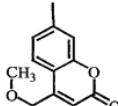
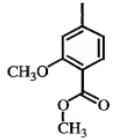
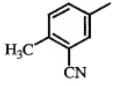
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
475		2-(2,3-Dihydro-1,4-benzodioxin-6-yl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.76 LCMS	51
476		Hexahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-1H-isoindole-1,3(2H)-dione.	0.31 LCMS	51
477		Hexahydro-2-(5-isoquinolinyl)-1H-isoindole-1,3(2H)-dione.	1.83 LCMS	51
478		Hexahydro-2-(2,4,5-trifluorophenyl)-1H-isoindole-1,3(2H)-dione.	0.27 LCMS	51
479		Hexahydro-2-(2,4,5-trichlorophenyl)-1H-isoindole-1,3(2H)-dione.	3.11 LCMS	51
480		Hexahydro-2-(2,3,4,6-tetrafluorophenyl)-1H-isoindole-1,3(2H)-dione.	3.10 LCMS	51
481		2-(3,4-Difluorophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	1.08 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
482		1-Acetyl-2,3-dihydro-6-(octahydro-1,3-dioxo-2H-isoindol-2-yl)-1H-indole.	2.58 LCMS	51
483		2-(3-Chloro-4-fluorophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.13 LCMS	51
484		2-(3,4-Dichlorophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	1.05 LCMS	51
485		Hexahydro-2-(3,4,5-trichlorophenyl)-1H-isoindole-1,3(2H)-dione.	3.63 LCMS	51
486		2-(3-Chloro-4-methoxyphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.99 LCMS	51
487		2-(3-Chloro-4-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.25 LCMS	51
488		Hexahydro-2-(2-methyl-1-naphthalenyl)-1H-isoindole-1,3(2H)-dione.	3.04 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
489		2-(4-Chloro-3-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.23 LCMS	51
490		2-(3,4-Dimethylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.07 LCMS	51
491		2-[4-Bromo-3-(trifluoromethyl)phenyl]hexahydro-1H-isoindole-1,3(2H)-dione.	1.23 LCMS	51
492		2-(4-Bromo-3-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.30 LCMS	51
493		2-(4-Fluoro-3-nitrophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.88 LCMS	51
494		2-[4-Fluoro-3-(trifluoromethyl)phenyl]hexahydro-1H-isoindole-1,3(2H)-dione.	1.23 LCMS	51
495		2-(4-Chloro-3-nitrophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.10 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		dione.		
496		2-[4-Chloro-3-(trifluoromethyl)phenyl]hexahydro-1H-isoindole-1,3(2H)-dione.	1.07 LCMS	51
497		2-(4-Chloro-2-methoxy-5-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.90 LCMS	51
498		2-(3-Fluoro-4-methoxyphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.80 LCMS	51
499		2-Bromo-5-(octahydro-1,3-dioxo-2H-isindol-2-yl)benzoic acid, methyl ester.	3.05 LCMS	51
500		Hexahydro-2-(4-methyl-3-nitrophenyl)-1H-isoindole-1,3(2H)-dione.	3.01 LCMS	51
501		Hexahydro-2-(3,4,5-trimethoxyphenyl)-1H-isoindole-1,3(2H)-dione.	2.65 LCMS	51
502		2-(3,4-Dimethoxyphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.58 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
503		Hexahydro-2-[2-(2-pyridinyl)-1H-benzimidazol-5-yl]-1H-isoindole-1,3(2H)-dione.	2.41 LCMS	51
504		2-(9-Ethyl-9H-carbazol-3-yl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.39 LCMS	51
505		Hexahydro-2-(2-methoxy-3-dibenzofuranyl)-1H-isoindole-1,3(2H)-dione.	3.17 LCMS	51
506		Hexahydro-2-(2,3,4-trifluorophenyl)-1H-isoindole-1,3(2H)-dione.	3.09 LCMS	51
507		Hexahydro-2-methyl-5-(octahydro-1,3-dioxo-2H-isoindol-2-yl)-1H-isoindole-1,3(2H)-dione.	2.29 LCMS	51
508		Hexahydro-2-[6-(methylthio)-5-nitro-8-quinoliny]-1H-isoindole-1,3(2H)-dione.	3.14 LCMS	51
509		2-[2,5-Dichloro-4-(1H-pyrrol-1-yl)phenyl]hexahydro-1H-isoindole-1,3(2H)-dione.	3.15 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
510		Hexahydro-2-(6-methyl-5-quinolinyl)-1H-isoindole-1,3(2H)-dione.	0.17 LCMS	51
511		N-(1,1-Dimethylethyl)-5-(octahydro-1,3-dioxo-2H-isoindol-2-yl)-1-naphthalenesulfonamide.	0.98 LCMS	51
512		Hexahydro-2-[4-(methoxymethyl)-2-oxo-2H-1-benzopyran-7-yl]-1H-isoindole-1,3(2H)-dione.	2.82 LCMS	51
513		2-(6-Benzothiazolyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.65 LCMS	51
514		2-Methoxy-4-(octahydro-1,3-dioxo-2H-isoindol-2-yl)benzoic acid, methyl ester.	2.82 LCMS	51
515		2-Methyl-5-(octahydro-1,3-dioxo-2H-isoindol-2-yl)benzonitrile.	2.85 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
516		Hexahydro-2-(2-oxo-2H-1-benzopyran-6-yl)-1H-isoindole-1,3(2H)-dione.	2.64 LCMS	51
517		Hexahydro-2-(2-methyl-8-quinolinyl)-1H-isoindole-1,3(2H)-dione.	1.10 LCMS	51
518		2-[3,5-Bis(trifluoromethyl)phenyl]hexahydro-1H-isoindole-1,3(2H)-dione.	3.51 LCMS	51
519		Hexahydro-2-(2,4,5-trimethylphenyl)-1H-isoindole-1,3(2H)-dione.	3.16 LCMS	51
520		2-(4-Fluoro-3-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.00 LCMS	51
521		Hexahydro-2-(3-methoxy-4-methylphenyl)-1H-isoindole-1,3(2H)-dione.	0.98 LCMS	51
522		N-Ethyl-2-methyl-5-(octahydro-1,3-dioxo-2H-isoindol-2-yl)-N-phenylbenzenesulfonamide.	3.01 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
523		2-(2,3-Dimethyl-1H-indol-5-yl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.97 LCMS	51
524		2-(3-Dibenzofuranyl)hexahydro-1H-isoindole-1,3(2H)-dione.	1.04 LCMS	51
525		2-(4-Bromophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.12 LCMS	51
526		2-(3-Chloro-4-nitrophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	0.98 LCMS	51
527		2-(1,3-Dihydro-2,2-dioxidobenzo[c]thiophen-5-yl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.30 LCMS	51
528		Hexahydro-2-(6-nitro-2-naphthalenyl)-1H-isoindole-1,3(2H)-dione.	3.213 LCMS	51
529		Hexahydro-2-(1H-indazol-5-yl)-1H-isoindole-1,3(2H)-dione.	2.45 LCMS	51

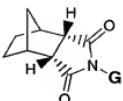
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
530		2-(4-Amino-2,3,5,6-tetrafluorophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.86 LCMS	51
531		2-(4-Bromo-3-chlorophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.37 LCMS	51
532		2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)hexahydro-1H-isoindole-1,3(2H)-dione.	2.73 LCMS	51
533		4-(Octahydro-1,3-dioxo-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile.	3.26 LCMS	51
534		Hexahydro-2-(9-oxo-9H-fluoren-1-yl)-1H-isoindole-1,3(2H)-dione.	3.07 LCMS	51
535		2-Fluoro-5-(octahydro-1,3-dioxo-2H-isoindol-2-yl)benzonitrile.	2.22 LCMS	51
536		Hexahydro-2-(9-oxo-9H-fluoren-2-yl)-1H-isoindole-1,3(2H)-dione.	0.23 LCMS	51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
537		2-(3-Chloro-4-iodophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.40 LCMS	51
538		2-(4-Bromo-2,3,5,6-tetrafluorophenyl)hexahydro-1H-isoindole-1,3(2H)-dione.	3.50 LCMS	51
539		Hexahydro-2-(2,3,5,6-tetramethyl-4-nitrophenyl)-1H-isoindole-1,3(2H)-dione.	3.22 LCMS	51
540		Hexahydro-2-(2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl)-1H-isoindole-1,3(2H)-dione.	3.43 LCMS	51
541		2-(3-Bromo-4-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.		51
542		2-(4-Bromo-2-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.		51
543		Hexahydro-2-(1-naphthalenyl)-1H-isoindole-1,3(2H)-dione.		51

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
544		2-(3-Chloro-2-methylphenyl)hexahydro-1H-isoindole-1,3(2H)-dione.		51

Examples 545 to 580

- 5 Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 545 to 580 have the following structure:



- 10 where G, the compound name, retention time, and the procedure employed, are set forth in **Table 6** (L is a bond for the compounds of **Table 6**).

The chromatography techniques used to determine the compound retention times of **Table 6** are as follows:

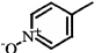
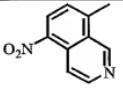
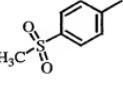
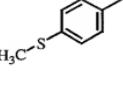
- LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 15 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- LCMS*** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.
- 20 The molecular mass of the compounds listed in **Table 6**, where provided, were determined by MS (ES) by the formula m/z.

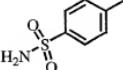
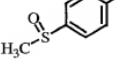
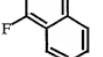
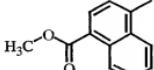
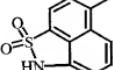
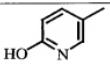
Table 6

<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
545		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-Hexahydro-2-(2-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	6.85	LCMS 39B
546		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-2-(2-Amino-4,5-dichlorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.62	LC 39B
547		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.47 & 3.58	39B
548		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-Hexahydro-2-(8-hydroxy-5-quinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.92	LC 39B
549		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-Hexahydro-2-(1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.30 & 3.44	39B
550		(3 α ,4 α ,7 α ,7 $\alpha\alpha$)-4-(Octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-1-naphthalenecarbonitrile.	3.29	LC 39B

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
551		(3a α ,4a α ,7a α ,7aa)-Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.76 LC	39B
552		(3a α ,4a α ,7a α ,7aa)-2-(4-Bromo-1-naphthalenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.93 LC	39B
553		(3a α ,4a α ,7a α ,7aa)-2-(2-Fluorenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	4.04 LC	39B
554		(3a α ,4a α ,7a α ,7aa)-Hexahydro-2-(2-methyl-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.56 LC	39B
555		(3a α ,4a α ,7a α ,7aa)-2-(3,5-Dichlorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.70 LCMS	39B
556		(3a α ,4a α ,7a α ,7aa)-2-(3-Chlorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.83 LCMS	39B

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
557		(3 α ,4 α ,7 α ,7 α)-2-(3-Chloro-4-fluorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.11	LCMS 39B
558		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.12	LCMS 39B
559		(3 α ,4 α ,7 α ,7 α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.57	LCMS 39B
560		(3 α ,4 α ,7 α ,7 α)-2-(4-Bromo-3-methylphenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.35	LCMS 39B
561		(3 α ,4 α ,7 α ,7 α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.48	LCMS 39B
562		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-(4-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.19	LC 39B

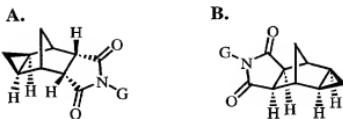
Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
563		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-(1-oxido-4-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.47	LC
564		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-(6-quinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.57	LC
565		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-(1-oxido-6-quinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.08	LCMS
566		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-(5-nitro-8-isoquinolinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione, trifluoroacetate (1:1).	2.59	LC
567		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-[4-(methylsulfonyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.03	LCMS
568		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-[4-(methylthio)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.79	LCMS

Ex. No.	<u>L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
569		(3a α ,4 α ,7 α ,7a α)-4-(Octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzenesulfonamide.	1.90 LCMS	39B
570		(3a α ,4 α ,7 α ,7a α)-Hexahydro-2-[4-(methylsulfinyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.98 LCMS	39B
571		(3a α ,4 α ,7 α ,7a α)-2-(4-Fluoro-1-naphthalenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.87 & 2.93 LCMS	39B
572		(3a α ,4 α ,7 α ,7a α)-4-(Octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-1-naphthalenecarboxylic acid, methyl ester.	2.92 & 3.02 LCMS	39B
573		(3a α ,4 α ,7 α ,7a α)-2-(1,1-Dioxido-2H-naphth[1,8-cd]isothiazol-5-yl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.28 & 2.43 LC	39B
574		(3a α ,4 α ,7 α ,7a α)-Hexahydro-2-(6-hydroxy-3-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.49 LCMS	39B

<u>Ex. No.</u>	<u>-L-G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure of <u>Example</u>
575		(3 α ,4 α ,7 α ,7 α)-2-(1,2-dimethyl-1,2-dihydrothieno[3,2-c]thiophen-3-yl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.59 LCMS	39B
576		(3 α ,4 α ,7 α ,7 α)-2-(3-benzofuranyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.04 LCMS	39B
577		(3 α ,4 α ,7 α ,7 α)-3-(Octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-2-benzofurancarboxylic acid, methyl ester.	3.08 LCMS	39B
578		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-[4-(4-isothiazolyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.74 LC	39B
579		(3 α ,4 α ,7 α ,7 α)-2-(3-Chloro-4-hydroxyphenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.36 LC	39B
580		(3 α ,4 α ,7 α ,7 α)-Hexahydro-2-[4-(1H-tetrazol-5-yl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione, trifluoroacetate (1:1).	2.13 LC	39B

Examples 581 to 588

- Additional compounds of the formula I were prepared by procedures 5 analogous to those described above. The compounds of Examples 581 to 588 have the following structure:



- 10 where G, the compound name, retention time, and the procedure employed, are set forth in **Table 7** (L is a bond for the compounds of **Table 7**).

The chromatography techniques used to determine the compound retention times of **Table 7** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over

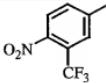
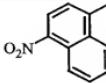
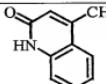
- 15 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

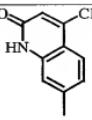
***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

- 20 The molecular mass of the compounds listed in **Table 7**, where provided, were determined by MS (ES) by the formula m/z.

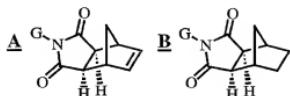
Table 7

Ex. No.	-L-G	A/B	Compound Name	Retention Time Min.	Procedure of Example
581		A	(3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.21	LC 10B
582		A	(3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.35	LC 10B
583		A	(3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	5.74 & 6.01	LC 10B
584		A	(3a α ,4 α ,4a β ,5a β ,6 α ,6a α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinal)-4,4a,5,5a,6,6a-hexahydro-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.59	LC 10B
585		B	(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.34	LC 11B

			1,3(2H,3aH)-dione.		
586		B	(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(3,5-Dichlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.68 LC	11B
587		B	(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.44 LC	11B
588		B	(3 α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)-4,4a,5,5a,6,6a-hexahydro-4,6-methanocycloprop[f]isoindole-1,3(2H,3aH)-dione.	2.77 LC	11B

Examples 589 to 601

Additional compounds of the formula I were prepared by procedures 5 analogous to those described above. The compounds of Examples 589 to 601 have the following structure:



where G, the compound name, retention time, and the procedure employed, are set 10 forth in **Table 8** (L is a bond for the compounds of **Table 8**).

The chromatography techniques used to determine the compound retention times of **Table 8** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

5 ***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

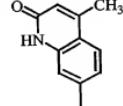
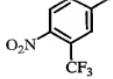
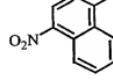
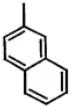
LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

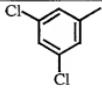
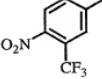
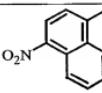
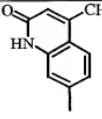
The molecular mass of the compounds listed in **Table 8**, where provided, were

10 determined by MS (ES) by the formula m/z.

Table 8

<u>Ex. No.</u>	<u>-L-G</u>	<u>A/B</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
589		A	(3 α ,4 β ,7 β ,7 α)-3a,4,7,7a-tetrahydro-2-(2-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.68 *LCMS	3B
590		B	(3 α ,4 β ,7 β ,7 α)-Hexahydro-2-(1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.57 *LCMS	4B
591		A	(3 α ,4 β ,7 β ,7 α)-2-(3,5-Dichlorophenyl)-3a,4,7,7a-tetrahydro-4,7-methano-	3.53 LCMS	3B

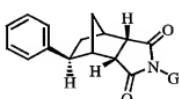
			1H-isoindole-1,3(2H)-dione.		
592		A	(3a α ,4 β ,7 β ,7a α)-3a,4,7,7a-Tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.16 LCMS	3B
593		A	(3a α ,4 β ,7 β ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.52 LCMS	3B
594		A	(3a α ,4 β ,7 β ,7a α)-3a,4,7,7a-Tetrahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.27 LCMS	3B
595		A	(3a α ,4 β ,7 β ,7a α)-3a,4,7,7a-Tetrahydro-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.01 LCMS	3B
596		B	(3a α ,4 β ,7 β ,7a α)-Hexahydro-2-(2-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	1.45 *LCMS	4B
597		B	(3a α ,4 β ,7 β ,7a α)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-	3.25 LC	4B

			1,3(2H)-dione.		
598		B	(3a α ,4 β ,7 β ,7a α)-2-(3,5-Dichlorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.64 LC	4B
599		B	(3a α ,4 β ,7 β ,7a α)-Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.41 LC	4B
600		B	(3a α ,4 β ,7 β ,7a α)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.13 & 3.22 LC	4B
601		B	(3a α ,4 β ,7 β ,7a α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.68 LC	4B

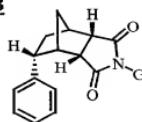
Examples 602 to 613

Additional compounds of the formula I were prepared by procedures
5 analogous to those described above. The compounds of Examples 602 to 613 have the following structure:

A



B



where G, the compound name, retention time, and the procedure employed, are set forth in **Table 9** (L is a bond for the compounds of **Table 9**).

5 The chromatography techniques used to determine the compound retention times of **Table 9** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

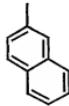
***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

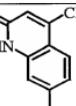
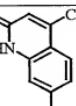
10 **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

The molecular mass of the compounds listed in **Table 9**, where provided, were determined by MS (ES) by the formula m/z.

15

Table 9

<u>Ex. No.</u>	<u>-L-G</u>	<u>A/B</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
602		A	(3 α ,4 α ,5 α ,7 α ,7a α)- Hexahydro-2-(2- naphthalenyl)-5-phenyl- 4,7-methano-1H- isoindole-1,3(2H)-dione.	1.95 *LCMS	7C
603		A	(3 α ,4 α ,5 α ,7 α ,7a α)- Hexahydro-5-phenyl-2-[3- (trifluoromethyl)phenyl]- 4,7-methano-1H- isoindole-1,3(2H)-dione.	1.94 *LCMS	7C

604		A	(3 α ,4 α ,5 α ,7 α ,7 $\alpha\alpha$)- Hexahydro-2-(1-naphthalenyl)-5-phenyl- 4,7-methano-1H- isoindole-1,3(2H)-dione.	1.83 *LCMS	7C
605		A	(3 α ,4 α ,5 α ,7 α ,7 $\alpha\alpha$)-2-(3,4-Dichlorophenyl)hexahydro- o-5-phenyl-4,7-methano- 1H-isoindole-1,3(2H)- dione.	1.97 *LCMS	7C
606		A	(3 α ,4 α ,5 α ,7 α ,7 $\alpha\alpha$)-2-(3,5-Dichlorophenyl)hexahydro- o-5-phenyl-4,7-methano- 1H-isoindole-1,3(2H)- dione.	2.03 *LCMS	7C
607		A	(3 α ,4 α ,5 α ,7 α ,7 $\alpha\alpha$)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)hexahydro-5-phenyl-4,7-methano-1H- isoindole-1,3(2H)-dione.	3.26 LCMS	7C
608		B	(3 α ,4 α ,5 β ,7 α ,7 $\alpha\alpha$)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)hexahydro-5-phenyl-4,7-methano-1H- isoindole-1,3(2H)-dione, trifluoroacetate (1:1).	1.62 *LCMS	9B

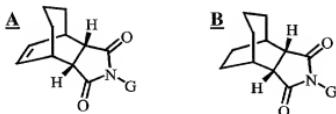
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609		B	(3 α ,4 α ,5 β ,7 α ,7a α)- Hexahydro-5-phenyl-2-[3-(trifluoromethyl)phenyl]- 4,7-methano-1H- isoindole-1,3(2H)-dione.	3.59	LCMS	9B
610		A	(3 α ,4 α ,5 α ,7 α ,7a α)- Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]- 5-phenyl-4,7-methano- 1H-isoindole-1,3(2H)- dione.	3.81	LCMS	7C
611		A	(3 α ,4 α ,5 α ,7 α ,7a α)- Hexahydro-2-(4-nitro-1-naphthalenyl)-5-phenyl- 4,7-methano-1H- isoindole-1,3(2H)-dione.	3.66	LCMS	7C
612		B	(3 α ,4 α ,5 β ,7 α ,7a α)- Hexahydro-2-(4-nitro-1-naphthalenyl)-5-phenyl- 4,7-methano-1H- isoindole-1,3(2H)-dione.	3.49	LCMS	9B
613		B	(3 α ,4 α ,5 β ,7 α ,7a α)- Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]- 5-phenyl-4,7-methano- 1H-isoindole-1,3(2H)- dione.	3.68	LCMS	9B

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Examples 614 to 621

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 614 to 621 have
5 the following structure:



where G, the compound name, retention time, and the procedure employed are set
10 forth in **Table 10** (L is a bond for the compounds of **Table 10**).

The chromatography techniques used to determine the compound retention times of **Table 10** are as follows:

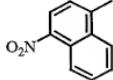
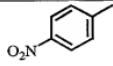
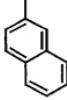
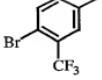
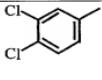
LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

15 ***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

20 The molecular mass of the compounds listed in **Table 10**, where provided, were determined by MS (ES) by the formula m/z.

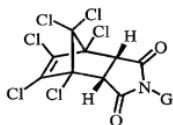
Table 10

<u>Ex. No.</u>	<u>-L-G</u>	<u>A/B</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
614		A	(3 α ,4 β ,8 β ,8 α)-4,5,6,7,8,8a-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	1.81 *LCMS	1B
615		A	(3 α ,4 β ,8 β ,8 α)-4,5,6,7,8,8a-Hexahydro-2-(4-nitrophenyl)-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	1.72 *LCMS	1B
616		A	(3 α ,4 β ,8 β ,8 α)-4,5,6,7,8,8a-Hexahydro-2-(2-naphthalenyl)-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	2.01 *LCMS	1B
617		A	(3 α ,4 β ,8 β ,8 α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-4,5,6,7,8,8a-hexahydro-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	2.04 *LCMS	1B
618		B	(3 α ,4 β ,8 β ,8 α)-2-(3,4-Dichlorophenyl)-4,5,6,7,8,8a-hexahydro-4,8-ethenocyclohepta[c]pyrrole-	2.09 *LCMS	2B

			1,3(2H,3aH)-dione.		
619		B	(3 α ,4 β ,8 β ,8a α)-4,5,6,7,8,8a-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	1.91 *LCMS	2B
620		A	(3 α ,4 β ,8 β ,8a α)-2-(3,4-Dichlorophenyl)-4,5,6,7,8,8a-hexahydro-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	1.94 *LCMS	1B
621		A	(3 α ,4 β ,8 β ,8a α)-2-(3,5-Dichlorophenyl)-4,5,6,7,8,8a-hexahydro-4,8-ethenocyclohepta[c]pyrrole-1,3(2H,3aH)-dione.	1.89 *LCMS	1B

Examples 622 to 635

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 622 to 635 have 5 the following structure:



where G, the compound name, retention time, and the procedure employed are set 10 forth in **Table 11** (L is a bond for the compounds of **Table 11**).

The chromatography techniques used to determine the compound retention times of **Table 11** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

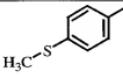
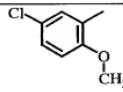
***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

- 5 **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

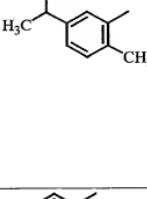
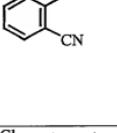
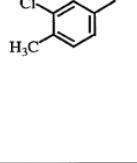
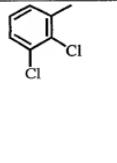
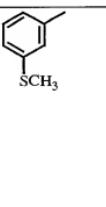
The molecular mass of the compounds listed in **Table 11**, where provided, were determined by MS (ES) by the formula m/z.

10

Table 11

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
622		(3a α ,4 α ,7 α ,7a α)-4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-2-(3-nitrophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		51
623		(3a α ,4 α ,7 α ,7a α)-4,5,6,7,8,8-Hexachloro-2-[4-(methylthio)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		51
624		(3a α ,4 α ,7 α ,7a α)-4,5,6,7,8,8-Hexachloro-2-(5-chloro-2-methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		51

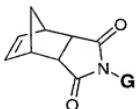
<u>Ex. No.</u>	<u>-L-G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
625		(3 α ,4 α ,7 α ,7a α)-4,5,6,7,8,8- Hexachloro-3a,4,7,7a- tetrahydro-2-(3- methoxyphenyl)-4,7- methano-1H-isoindole- 1,3(2H)-dione.		51
626		(3 α ,4 α ,7 α ,7a α)-4,5,6,7,8,8- Hexachloro-3a,4,7,7a- tetrahydro-2-(1- naphthalenyl)-4,7-methano- 1H-isoindole-1,3(2H)-dione.		51
627		(3 α ,4 α ,7 α ,7a α)-4,5,6,7,8,8- Hexachloro-2-(2,3- dimethylphenyl)-3a,4,7,7a- tetrahydro-4,7-methano-1H- isoindole-1,3(2H)-dione.		51
628		(3 α ,4 α ,7 α ,7a α)-4,5,6,7,8,8- Hexachloro-2-(3,4- dichlorophenyl)-3a,4,7,7a- tetrahydro-4,7-methano-1H- isoindole-1,3(2H)-dione.		51
629		(3 α ,4 α ,7 α ,7a α)-2-(4- Bromophenyl)-4,5,6,7,8,8- hexachloro-3a,4,7,7a- tetrahydro-4,7-methano-1H- isoindole-1,3(2H)-dione.		51

Ex. No.	<u>-L-G</u>	Compound Name	Retention Time Min.	Procedure of Example
630		(3 α ,4 α ,7 α ,7 α)-4,5,6,7,8,8- Hexachloro-3 α ,4,7,7 α - tetrahydro-2-[2-methyl-5-(1- methylethyl)phenyl]-4,7- methano-1H-isoindole- 1,3(2H)-dione.		51
631		(3 α ,4 α ,7 α ,7 α)-N-(2- cyanophenyl)-1,4,5,6,7,7- hexachloro-5-norbornene- 2,3-dicarboximide		51
632		(3 α ,4 α ,7 α ,7 α)-4,5,6,7,8,8- Hexachloro-2-(3-chloro-4- methylphenyl)-3 α ,4,7,7 α - tetrahydro-4,7-methano-1H- isoindole-1,3(2H)-dione.		51
633		(3 α ,4 α ,7 α ,7 α)-4,5,6,7,8,8- Hexachloro-2-(2,3- dichlorophenyl)-3 α ,4,7,7 α - tetrahydro-4,7-methano-1H- isoindole-1,3(2H)-dione.		51
634		(3 α ,4 α ,7 α ,7 α)-4,5,6,7,8,8- Hexachloro-3 α ,4,7,7 α - tetrahydro-2-[3- (methylthio)phenyl]-4,7- methano-1H-isoindole- 1,3(2H)-dione.		51

<u>Ex. No.</u>	<u>-L-G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure <u>of Example</u>
635		(3a α ,4 α ,7 α ,7a α)-4,5,6,7,8,8- Hexachloro-2-(4-fluoro-3- nitrophenyl)-3a,4,7,7a- tetrahydro-4,7-methano-1H- isoindole-1,3(2H)-dione.		51

Examples 636 to 679

- 5 Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 636 to 679 have the following structure:



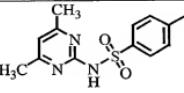
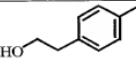
- 10 where G, the compound name, retention time and the procedure employed are set forth in **Table 12** (L is a bond for the compounds of **Table 12**).
- The chromatography techniques used to determine the compound retention times of **Table 12** are as follows:
- LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 15 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- ***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

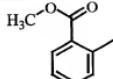
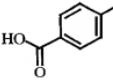
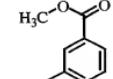
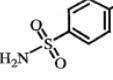
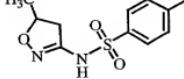
The molecular mass of the compounds listed in **Table 12**, where provided, were determined by MS (ES) by the formula m/z.

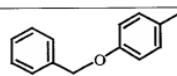
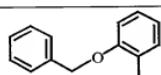
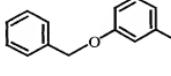
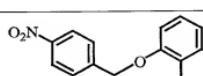
Table 12

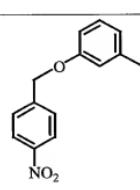
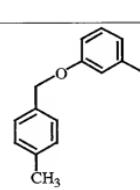
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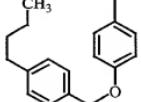
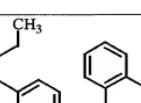
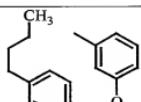
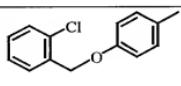
Ex. <u>No.</u>	<u>G</u>	Compound <u>Name</u>	Retention Time <u>Min.</u>	Procedure of <u>Example</u>
636		3a,4,7,7a-Tetrahydro-2-(6-methyl-2-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
637		3a,4,7,7a-Tetrahydro-2-(4-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
638		2-(4-Ethoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
639		3a,4,7,7a-Tetrahydro-2-(3-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
640		3a,4,7,7a-Tetrahydro-2-(2-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	

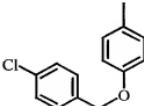
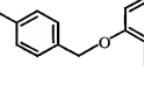
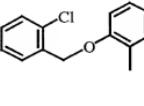
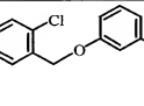
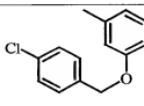
Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
641		3a,4,7,7a-Tetrahydro-2-(3-methyl-2-pyridinyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
642		N-(4,6-Dimethyl-2-pyrimidinyl)-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzenesulfonamide.		25D or 38A
643		3a,4,7,7a-Tetrahydro-2-[4-(2-hydroxyethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
644		3a,4,7,7a-Tetrahydro-2-(2-mercaptophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
645		2-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzoic acid.		25D or 38A

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
646		2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzoic acid, methyl ester.		25D or 38A
647		4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzoic acid.		25D or 38A
648		3-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzoic acid, methyl ester.		25D or 38A
649		4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzenesulfonamide.		25D or 38A
650		N-(4,5-Dihydro-5-methyl-3-isoxazolyl)-4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzenesulfonamide.		25D or 38A

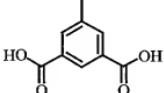
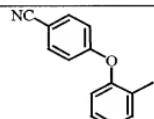
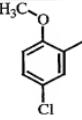
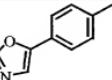
Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
651		3a,4,7,7a-Tetrahydro-2-(2-hydroxyphenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
652		3a,4,7,7a-Tetrahydro-2-[4-(phenylmethoxy)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
653		3a,4,7,7a-Tetrahydro-2-[2-(phenylmethoxy)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
654		3a,4,7,7a-Tetrahydro-2-[3-(phenylmethoxy)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
655		3a,4,7,7a-Tetrahydro-2-[4-[(4-nitrophenyl)methoxy]phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
656		3a,4,7,7a-Tetrahydro-2-[2-[(4-nitrophenyl)methoxy]phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
		henyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		38A
657		3a,4,7,7a-Tetrahydro-2-[3-[(4-nitrophenyl)methoxy]phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
658		3a,4,7,7a-Tetrahydro-2-[4-[(4-methylphenyl)methoxy]phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
659		3a,4,7,7a-Tetrahydro-2-[3-[(4-methylphenyl)methoxy]phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
660		3a,4,7,7a-Tetrahydro-2-[2-[(4-methylphenyl)methoxy]phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
661		2-[4-[(4-Butylphenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
662		2-[2-[(4-Butylphenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
663		2-[3-[(4-Butylphenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
664		2-[4-[(2-Chlorophenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
665		2-[4-[(4-Chlorophenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
666		2-[2-[(4-Chlorophenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
667		2-[2-[(2-Chlorophenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
668		2-[3-[(2-Chlorophenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
669		2-[3-[(4-Chlorophenyl)methoxy]phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
		tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	38A	
670		3a,4,7,7a-Tetrahydro-2-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
671		2-[(Benzoyloxy)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
672		2-[3-(3,4-Dimethylbenzoyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
673		2-(3,4-Dimethylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	25D or 38A	
674		4-(1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzoic acid, ethyl ester.	25D or 38A	

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
675		5-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)-1,3-benzenedioic acid.		25D or 38A
676		4-[2-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)phenoxy]benzonitrile		25D or 38A
677		2-(5-Chloro-2-methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
678		2-(2-Acetylphenyl)-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A
679		3a,4,7,7a-Tetrahydro-2-[4-(5-oxazolyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		25D or 38A

Examples 680 to 702

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Examples 680 to 702 have the structures, compound names, retention times, and were prepared by the procedures 5 indicated in **Table 13**.

The chromatography techniques used to determine the compound retention times of **Table 13** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

10 ***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

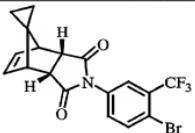
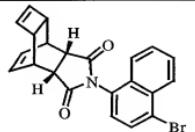
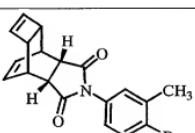
LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

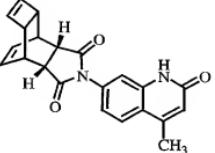
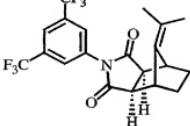
15 The molecular mass of the compounds listed in **Table 13**, where provided, were determined by MS (ES) by the formula m/z.

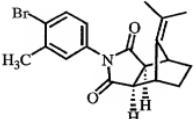
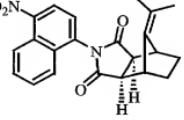
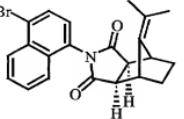
ND = no data provided; compound was unstable under chromatography conditions employed

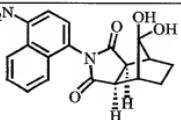
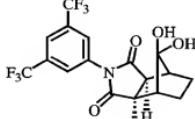
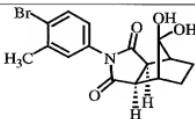
Table 13

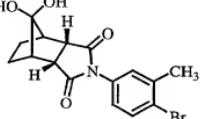
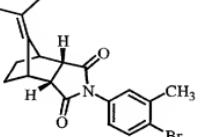
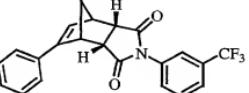
<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
680		(3 α ,4 α ,7 α ,7 α)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3 α ,4,7,7 α -tetrahydro-5-methyl-4,7-methano-1H-	7.72 <u>LCMS</u>	30

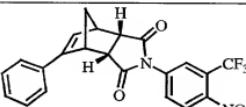
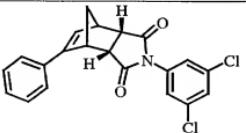
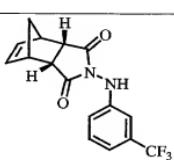
Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
		isoindole- 1,3(2H)-dione.		
681		(3a α ,4 α ,7 α ,7a α)- 2'-(4-Bromo-3-(trifluoromethyl) phenyl)- 3a',4',7',7a'- tetrahydrospiro[cyclopropane- 1,8'- [4,7]methano[1 H]isoindole]- 1',3'(2H)-dione.	3.45 LC	12B
682		(3a α ,4 β ,4a α 6a α ,7 β ,7a α)-2- (4-Bromo-1- naphthalenyl)- 3a,4,4a,6a,7,7a- hexahydro-4,7- etheno-1H- cyclobut[f]isoind ole-1,3(2H)- dione.	3.597 LC	29
683		(3a α ,4 β ,4a α 6a α ,7 β ,7a α)-2- (4-Bromo-3- methylphenyl)- 3a,4,4a,6a,7,7a- hexahydro-4,7- etheno-1H- cyclobut[f]isoind ole-1,3(2H)- dione.	3.61 LC	29

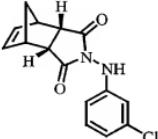
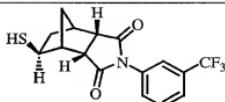
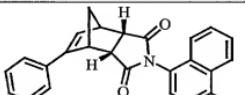
Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
		3a,4,4a,6a,7,7a-hexahydro-4,7-etheno-1H-cyclobut[f]isoindole-1,3(2H)-dione.		
684		(3a α ,4 β ,4a α)-6a α ,7 β ,7a α)-2-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)-3a,4,4a,6a,7,7a-hexahydro-4,7-etheno-1H-cyclobut[f]isoindole-1,3(2H)-dione.	2.73 LC	29
685		(3a α ,4 β ,7 β ,7a α)-2-[3,5-Bis(trifluoromethyl)phenyl]hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione.	4.50 LC	31B

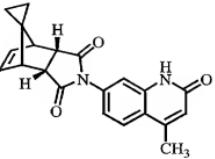
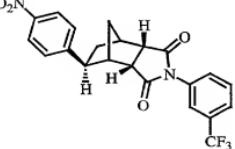
Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
686		(3a α ,4 β ,7 β ,7a α)-2-(4-Bromo-3-methylphenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione.	4.27 LC	31B
687		(3a α ,4 β ,7 β ,7a α)-Hexahydro-8-(1-methylethylidene)-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.	4.06 LC	31B
688		(3a α ,4 β ,7 β ,7a α)-2-(4-Bromo-1-naphthalenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione.	4.30 LC	31B

Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
689		(3 α ,4 β ,7 β ,7 α)- Hexahydro-8,8- dihydroxy-2-(4- nitro-1- naphthalenyl)- 4,7-methano- 1H-isoindole- 1,3(2H)-dione.	ND	32
690		(3 α ,4 β ,7 β ,7 α)- 2-[3,5- Bis(trifluoromethyl- phenyl)hexa- hydro-8,8- dihydroxy-4,7- methano-1H- isoindole- 1,3(2H)-dione.	ND HRMS (ESI): m/z 408.066	32
691		(3 α ,4 β ,7 β ,7 α)- 2-(4-Bromo-3- methylphenyl)h- exahydro-8,8- dihydroxy-4,7- methano-1H- isoindole- 1,3(2H)-dione.	HRMS (ESI): m/z 364.019	32

Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
692		(3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)hexahydro-8,8-dihydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione.	ND	18
693		(3a α ,4 α ,7 α ,7a α)-2-(4-Bromo-3-methylphenyl)hexahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione.	4.35 LC	17B
694		(3a α ,4 α ,7 α ,7a α)-3a,4,7,7a-Tetrahydro-5-phenyl-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.57 LC	8C

Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
695		(3a α ,4a,7a,7a α)-3a,4,7,7a-Tetrahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.69	LC
696		(3a α ,4a,7a,7a α)-2-(3,5-Dichlorophenyl)-3a,4,7,7a-Tetrahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.86	LC
697		(3a α ,4a,7a,7a α)-Tetrahydro-2-[3-(trifluoromethyl)phenyl]amino]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.00	LC

Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
698		(3a α ,4 α ,7a α ,7a α)-2-[(3-Chlorophenyl)amino]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.	2.78 LC	35
699		(3a α ,4 α ,5 α ,7 α ,7 α α)-Hexahydro-5-mercaptop-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.19 LC	43B
700		(3a α ,4 α ,7 α ,7 α α)-3a,4,7,7a-Tetrahydro-2-(4-nitro-1-naphthalenyl)-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.51 LC	8C

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
701		(3a'α,4'α,7α,7a')- α -2'-(1,2-Dihydro-4-methyl-2-oxo-7-quinolinyl)- 3a',4',7',7a'-tetrahydrospiro[cyclopropane-1,8'-[4,7]methano[1H]isoindole]-1',3'(2H)-dione.	2.66	LC 12B
702		(3aα,4α,5α,7α,7aα)-Hexahydro-5-(4-nitrophenyl)-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.	3.60	LCMS 7C

Examples 703 to 755

Additional compounds of the formula I can be prepared by procedures analogous to those described above. The compounds of Examples 703 to 755 have the structures, compound names, and retention times, and can be prepared by the procedure indicated in **Table 14**.

The chromatography techniques used to determine the compound retention times of **Table 14** are as follows:

LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

10 *LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

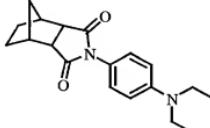
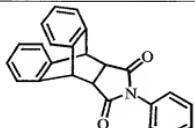
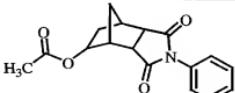
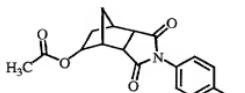
LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

The molecular mass of the compounds listed in **Table 14**, where provided, were

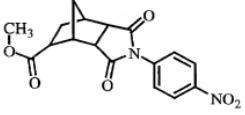
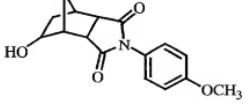
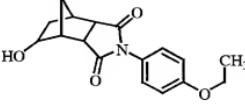
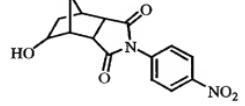
15 determined by MS (ES) by the formula m/z.

Table 14

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
703		Hexahydro-2-(2-mercaptophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		39B
704		4-(Octahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl)benzoic acid,		39B

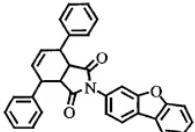
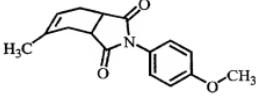
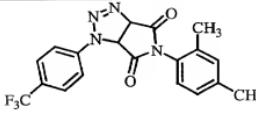
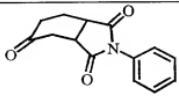
<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethyl ester.		
705		2-[4-(Diethylamino)phenyl]hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		39B
706		3a,4,9,9a-Tetrahydro-2-phenyl-4,9[1',2']-benzeno-1H-benz[f]isoindole-1,3(2H)-dione.		
707		5-(Acetoxy)hexahydro-2-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.		
708		5-(Acetoxy)-2-(4-chlorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		

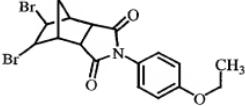
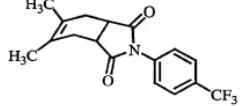
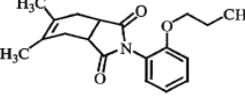
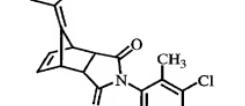
<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
709		5-(Acetoxy)hexahydro-2-(2-nitrophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		
710		5-(Acetoxy)-2-(3-chlorophenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		
711		Octahydro-2-(4-methoxyphenyl)-1,3-dioxo-4,7-methano-1H-isoindole-5-carboxylic acid, methyl ester.		
712		2-(2,4-Dichlorophenyl)octahydro-1,3-dioxo-4,7-methano-1H-isoindole-5-carboxylic acid, methyl ester.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
713		Octahydro-2-(4-nitrophenyl)-1,3-dioxo-4,7-methano-1H-isoindole-5-carboxylic acid, methyl ester.		
714		Hexahydro-5-hydroxy-2-(4-methoxyphenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		
715		2-(4-Ethoxyphenyl)hexahydro-5-hydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione.		
716		Hexahydro-5-hydroxy-2-(4-nitrophenyl)-4,7-methano-1H-isoindole-1,3(2H)-dione.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
717		2-(4-Chlorophenyl)hexahydro-5-hydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione.		
718		2-(2,4-Dichlorophenyl)hexahydro-5-hydroxy-4,7-methano-1H-isoindole-1,3(2H)-dione.		
719		Hexahydro-5-hydroxy-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		
720		5-(Acetoxy)hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		

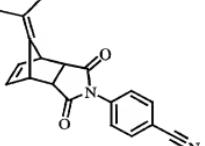
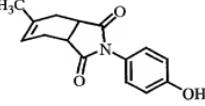
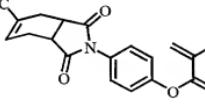
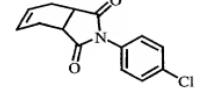
<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		isoindole-1,3(2H)-dione.		
721		2-Hydroxy-5-(octahydro-1,3-dioxo-5-phenyl-1H-isoindol-2-yl)benzoic acid.		
722		Hexahydro-2-(4-hydroxyphenyl)-5-phenyl-1H-isoindole-1,3(2H)-dione.		
723		2-(4-Ethoxyphenyl)hexahydro-5-phenyl-1H-isoindole-1,3(2H)-dione.		
724		Hexahydro-5-phenyl-2-[3-(trifluoromethyl)phenyl]-1H-isoindole-1,3(2H)-dione.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
725		2-(3-dibenzofuranyl)-3a,4,7,7a-tetrahydro-4,7-diphenyl-1H-isoindole-1,3(2H)-dione.		
726		3a,4,7,7a-Tetrahydro-2-(4-methoxyphenyl)-5-methyl-1H-isoindole-1,3(2H)-dione.		
727		5-(2,4-Dimethylphenyl)-1,6a-dihydro-1-[4-(trifluoromethyl)phenyl]pyrrolo[3,4-d]-1,2,3-triazole-4,6(3aH,5H)-dione.		
728		Tetrahydro-2-phenyl-1H-isindole-1,3,5(2H,4H)-trione.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
729		5,6-Dibromo-2-(4-ethoxyphenyl)hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione.		
730		3a,4,7,7a-Tetrahydro-5,6-dimethyl-2-[4-(trifluoromethyl)phenyl]-1H-isoindole-1,3(2H)-dione.		
731		3a,4,7,7a-Tetrahydro-5,6-dimethyl-2-(2-propoxypyhenyl)-1H-isoindole-1,3(2H)-dione.		
732		2-(3-Chloro-2-methylphenyl)-3a,4,7,7a-tetrahydro-8-(1-methylethylidene)-4,7-methano-1H-isoindole-1,3(2H)-dione.		17A 17B

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
733		3a,4',7,7'a-Tetrahydro-2-(2,4,6-trimethylphenyl)piro[cyclopropane-1,8'-[4,7]methano[1H]isoindole]-1',3'(2H)-dione.		12B
734		3a,4,7,7'a-Tetrahydro-4-methyl-2-(3-methylphenyl)-1H-isindole-1,3(2H)-dione.		
735		Hexahydro-2-[4-(2-methyl-5-phenyl-1,3,4-thiadiazol-2-yl)phenyl]-1H-isindole-1,3(2H)-dione.		
736		3a,4,7,7'a-Tetrahydro-5-methyl-2-[4-(trifluoromethyl)phenyl]-4,7-dione.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		methano-1H-isoindole-1,3(2H)-dione.		
737		3a,4,7,7a-Tetrahydro-5-methyl-2-[4-(trifluoromethoxy)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		
738		2-(3-Chloro-4-fluorophenyl)hexahydro-5-methyl-1H-isoindole-1,3(2H)-dione.		
739		3a,4,7,7a-Tetrahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	Retention Time Min.	Procedure of Example
740		4-[1,3,3a,4,7,7a-hexahydro-8-(1-methylethylidene)-1,3-dioxo-4,7-methano-2H-isoindol-2-yl]benzonitrile.		17A 17B
741		3a,4,7,7a-tetrahydro-2-(4-hydroxyphenyl)-1H-isindole-1,3(2H)-dione.		
742		2-Methyl-2-propenoic acid, 4-(1,3,3a,4,7,7a-hexahydro-5-methyl-1,3-dioxo-2H-isindol-2-yl)phenyl ester.		
743		2-(4-chlorophenyl)-3a,4,7,7a-tetrahydro-1H-isindole-1,3(2H)-dione.		

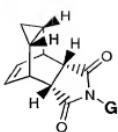
<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
744		4-(1,3,3a,4,7,7a-hexahydro-1,3-dioxo-2H-isoindol-2-yl)benzenesulfonamide.		
745		3a,4,7,7a-tetrahydro-2-phenyl-1H-isoindole-1,3(2H)-dione.		
746		3a,4,7,7a-tetrahydro-2-(2-mercaptophenyl)-1H-isoindole-1,3(2H)-dione.		
747		3a,4,7,7a-tetrahydro-2-[3-(methylthio)phenyl]-1H-isoindole-1,3(2H)-dione.		
748		2-(4-ethoxyphenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione.		

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
749		4,4a,5,5a,6,6a-hexahydro-2-[3-(trifluoromethyl)phenyl]-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)-dione.		5B
750		3'a,4',7',7'a-tetrahydro-2'-(4-nitrophenyl)spiro[cyclopropane-1,8'-[4,7]methano[1H]isoindole]-1',3'(2'H)-dione.		1B
751		2-hydroxy-5-(octahydro-1,3-dioxo-5-phenyl-4,7-methano-1H-isoindol-2-yl)benzoic acid.		7C 9B
752		4-(Octahydro-1,3-dioxo-5-phenyl-4,7-methano-1H-isoindol-2-yl)benzenesulfonamide.		7C 9B

<u>Ex. No.</u>	<u>Structure</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
753		Hexahydro-2-(4-hydroxyphenyl)-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.		7C 9B
754		2-(4-Ethoxyphenyl)hexahydro-5-phenyl-4,7-methano-1H-isoindole-1,3(2H)-dione.		7C 9B
755		Hexahydro-5-phenyl-2-[3-(trifluoromethyl)phenyl]-4,7-methano-1H-isoindole-1,3(2H)-dione.		7C 9B

Examples 756 to 763

Additional compounds of the formula I were prepared by procedures analogous to those described above. The compounds of Example 756 to 763 have the following structure:



where G, the compound name, retention time, and the procedure employed, are set forth in **Table 15** (L is a bond for the compounds of **Table 15**).

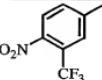
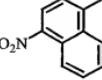
- 5 The chromatography techniques used to determine the compound retention times of **Table 15** are as follows:
- LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- ***LCMS** = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H₂O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.
- 10 **LC** = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H₂O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.
- The molecular mass of the compounds listed in **Table 15**, where provided, were determined by MS (ES) by the formula m/z.

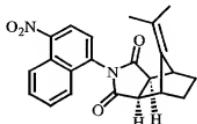
15

Table 15

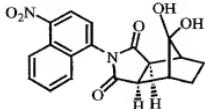
Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
756		(3a α ,4 β ,4a α ,5a α ,6 β ,6a α)-2-(3,4-Dichlorophenyl)-4,4a,5,5a,6,6a-hexahydro-4,6-ethenocycloprop[fl]isoindole-1,3(2H,3aH)-dione.	1.85	LCMS

Ex. No.	G	Compound Name	Retention Time Min.	Procedure of Example
757		$(3\alpha,4\beta,4a\alpha,5\alpha,6\beta,6a\alpha)-2-(3,5\text{-Dichlorophenyl})-4,4a,5,5a,6,6a\text{-hexahydro-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)\text{-dione.}}$	1.91	LCMS 5B
758		$(3\alpha,4\beta,4a\alpha,5\alpha,6\beta,6a\alpha)-2-(4\text{-Bromo-3-methylphenyl})-4,4a,5,5a,6,6a\text{-hexahydro-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)\text{-dione.}}$	1.83	LCMS 5B
759		$(3\alpha,4\beta,4a\alpha,5\alpha,6\beta,6a\alpha)-4,4a,5,5a,6,6a\text{-Hexahydro-2-(1-naphthalenyl)-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)\text{-dione.}}$	1.77	LCMS 5B
760		$(3\alpha,4\beta,4a\alpha,5\alpha,6\beta,6a\alpha)-4,4a,5,5a,6,6a\text{-Hexahydro-2-(2-naphthalenyl)-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)\text{-dione.}}$	1.64	LCMS 5B
761		$(3\alpha,4\beta,4a\alpha,5\alpha,6\beta,6a\alpha)-2-(1,2\text{-Dihydro-4-methyl-2-oxo-7-quinolinyl})-4,4a,5,5a,6,6a\text{-hexahydro-4,6-}$	2.79	LC 5B

<u>Ex. No.</u>	<u>G</u>	<u>Compound Name</u>	<u>Retention Time Min.</u>	<u>Procedure of Example</u>
		ethenocycloprop[f]isoindole-1,3(2H,3aH)-dione.		
762		(3 α ,4 β ,4a α ,5 α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.49 LC	5B
763		(3 α ,4 β ,4a α ,5 α ,6 β ,6a α)-4,4a,5,5a,6,6a-Hexahydro-2-[4-nitro-1-naphthalenyl]-4,6-ethenocycloprop[f]isoindole-1,3(2H,3aH)-dione.	3.30 LC	5B

Example 764(3 α ,4 β ,7 β ,7 α)-Hexahydro-8-(1-methylethylidene)-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoundole-1,3(2H)-dione (764)

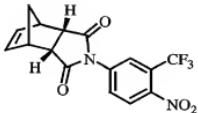
5 Compound **31A** (0.247 g, 1.20 mmol) and 4-nitro-1-naphthalamine (0.188 g, 1.00 mmol) were dissolved in AcOH (2.0 mL) and then heated at 105°C for 15 h. The reaction was allowed to cool to 25°C and then the AcOH was removed *in vacuo*. The resulting slurry was added to cold sat K₂CO₃ and stirred vigorously for 15 min. The suspension was then filtered and rinsed with water. The crude product was
10 purified by flash chromatography on SiO₂ eluting with 20% hexanes/methylene chloride affording 0.322 g of compound **764** as a yellow solid. HPLC: 92.4% at 4.063 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 765(3 α ,4 β ,7 β ,7 α)-Hexahydro-8,8-dihydroxy-2-(4-nitro-1-naphthalenyl)-4,7-methano-1H-isoundole-1,3(2H)-dione (765)

15 Compound **764** (0.214 g, 0.570 mmol) was dissolved in CCl₄ (10.0 mL)
20 and methylene chloride (2.0 mL) and cooled to -25°C. O₃ was then bubbled through the reaction until a blue color persisted (~10 min). DMS (0.418 mL, 5.70 mmol) was then added and the reaction warmed to 25°C. After 12 h, a white precipitate formed and was filtered, rinsing with CCl₄ and dried to yield 0.171 g of compound **765**. The precipitate was shown to be 95% pure by H¹ NMR spectroscopy, but was not stable to reverse phase LC conditions. HRMS (ESI): m/z 367.0932 [M- H]⁺. ¹H NMR Data:

Compound **765** is a mixture of atropisomers at 25°C, signals reported as major, minor or both (overlapping) atropisomers. ¹H NMR (Joel, 500 MHz, DMSO-d6, 25°C) δ 1.35 (2H, m, both); 1.94 (2H, m, both); 2.23 (2H, s, major); 2.29 (2H, s, minor); 3.01 (2H, s, minor); 3.12 (2H, s, major); 6.23 (1H, s, major); 6.31 (1H, s, minor); 6.55 (1H, s, major); 6.82 (1H, s, minor); 7.45 (1H, d, *J* = 7.7 Hz, major); 7.60 (1H, d, *J* = 8.3 Hz, minor); 7.73-7.88 (2H, m, both); 8.04 (1H, d, *J* = 8.2 Hz, major); 8.35-8.44 (2H, m, both).

10

Example 766**(3a α ,4 α ,7 α ,7a α)-2-[4-Nitro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-methano-1H-isoindole-1,3(2H)-dione (766)**

Compound **766** was synthesized as described in Example **38A**. HPLC: 15 96.2% at 3.03 min (retention time) (YMC ODSA S5 C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% CF₃COOH, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 352.1 [M + H]⁺.